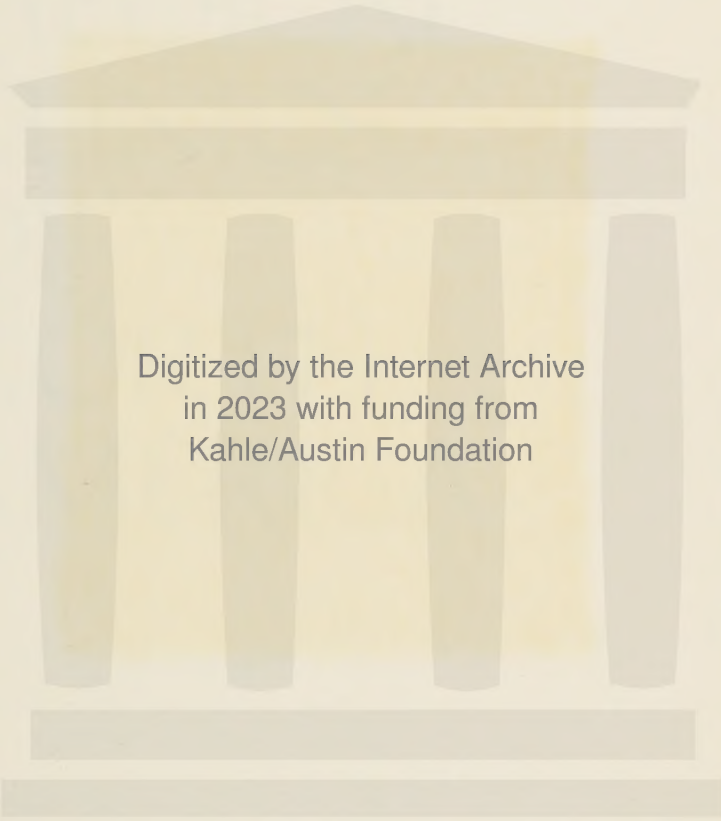


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SYMPOSIUM ON
DISEASES OF THE KIDNEY

Robert M. Kark, M.D., *Guest Editor*

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Foreword

This issue of the *Medical Clinics* reviews a broad field of medicine of increasing interest and importance. The internist in the seventies will rapidly broaden the base of his practice if he has not done so previously. His concept of what constitutes adequate care for the patient and the patient's family is changing. He will become increasingly concerned with the early detection of disease and with the prevention of chronic as well as acute noxious processes; with protection of his patients from environmental stresses and poisons; with attempts to guide patients to solve social and sexual problems, inimical to health; with the delivery of health care, particularly the thorough investigation of disease in an out-patient setting instead of in an expensive hospital ward. Chronic renal disease can be a terrible financial, emotional, and socially destructive burden to the patient and his family. We must find ways to change this.

This Chicago number of the *Medical Clinics of North America* is of some interest because it comes, in the main, from the revived Rush Medical College, which was founded in 1837 and which joined the University of Illinois Medical College some 30 years ago. The revived Rush Medical College has come into being now because of the demands for physicians to look after an expanding populace in Illinois. Nearly all the authors of the papers in this issue are or were connected with the Rush-Presbyterian St. Luke's Medical Center, and we trust you will benefit from their contributions.

ROBERT M. KARK, M.D.
Guest Editor

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Anemia of Renal Failure

*Walter Fried, M.D.**

Development of methods for chronic dialysis and for renal transplantation has resulted in prolonged survival of large numbers of patients with nonfunctioning kidneys and also of anephric patients. As a consequence, understanding and therapy of the complications of renal failure has become increasingly important. Anemia is one of the problems which invariably occur in patients with chronic renal failure. This paper will review the clinical characteristics of the anemia associated with renal failure, some of the current concepts of the pathogenesis of this anemia, and currently available and prospective methods of therapy.

CLINICAL CHARACTERISTICS OF THE ANEMIA OF RENAL FAILURE

Anemia occurs eventually in all patients with renal failure. Although studies of large numbers of patients indicate a correlation between the severity of anemia and the degree of uremia, there is wide variation in the time of onset and progression of anemia among individual patients.^{1, 6, 36, 42, 53} and there is no apparent relationship between these factors and the etiology of the renal disease. The erythrocytes of patients with anemia of renal disease are normochromic and normocytic,^{6, 36, 42} unless the anemia is complicated by iron deficiency.^{1, 42} On blood smear, most of the red cells appear normal. However "burr"⁵⁵ cells or schistocytes may be seen.⁴ The number of "burr" cells in the blood smear is related to the degree of uremia.⁵⁵ On the other hand, schistocytes are found primarily in association with lesions which affect the small blood vessels, such as periarteritis, nephrosclerosis, and hemolytic uremic syndrome. Their number is correlated with the severity of the vascular disease and the amount of hemolysis, but not necessarily with the degree of uremia.⁴

The number of reticulocytes and polychromatic red blood cells is inversely related to the severity of the anemia, but is always less than the number found in comparably anemic patients without impaired

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erythropoiesis. Even in severe anemias, these cells rarely occur in supernormal numbers.^{1, 6, 36, 42}

The bone marrow aspirate is normally cellular.⁶ Cells of the myeloid and megakaryocytic series are present in normal numbers and show no abnormalities of maturation.⁶ Erythropoiesis varies inversely with the severity of the anemia. However, the amount of erythroid activity in the marrow is less than that which occurs in comparably anemic patients without impaired erythropoiesis, and rarely exceeds normal activity.^{12, 42, 52, 59} The maturation pattern of the erythroid cells is undisturbed unless the anemia is complicated by iron deficiency. In uncomplicated cases, the marrow iron stores are increased.

The iron and iron binding globulin levels in the serum usually reflect the status of the iron stores.^{17, 36, 42} However, low serum iron levels occur at times, even though the iron stores are normal or increased.

The life span of erythrocytes is usually shortened in patients with moderate to severe uremia.^{8, 17, 35, 39, 42, 56, 57} Red cell survival correlates roughly with plasma urea content, and is shortest in patients with oliguria due to acute renal shutdown and in patients with chronic renal disease during periods of rapid progression of uremia.^{8, 56} Dialysis has no detectable effect on the survival of red cells in patients with significant hemolysis.^{35, 56}

Hemolysis is primarily the result of an extracorporeal defect, in that erythrocytes from uremic donors survive normally when transfused into normal patients^{8, 15} (with a few exceptions^{56, 57}) and erythrocytes from normal donors have a shortened survival time when injected into uremic patients. Hemolysis is primarily intravascular. Excess sequestration of red cells in the liver or spleen does not occur, and serum haptoglobin is often reduced in amount or undetectable.⁵⁶

Ferrokinetic studies performed on uremic patients characteristically show a decrease in the plasma iron clearance rate and in the rate of the incorporation of iron into newly formed red cells, relative to what would be expected from a comparably anemic patient with unimpaired erythropoiesis.^{17, 18, 35, 39, 42, 43} Significant ineffective erythropoiesis has not been observed.⁵⁵

In summary, anemia occurs in patients with renal failure primarily because of an inability of the marrow to produce a sufficient number of red cells to maintain a normal circulating red cell mass. It should be stressed that the various indices of erythropoiesis (reticulocyte count, ferrokinetics, and marrow erythroid activity) may be normal or even slightly elevated in severely anemic patients, but are always markedly decreased relative to what one would expect if the marrow were responding normally to the anemia. This defect is often complicated, particularly when uremia is progressing rapidly, by a mild to moderate intravascular hemolysis due to an extracorporeal abnormality. Iron deficiency may further complicate the anemia.

PATHOGENESIS OF THE ANEMIA OF RENAL FAILURE

The association of polycythemia with renal tumors^{3, 9, 13} and of anemia with severe renal impairment suggests that the kidneys play a role

in the regulation of erythropoiesis. This role was clarified by Jacobson and co-workers,³⁴ who reported in 1957 that nephrectomized rats were unable to increase their plasma erythropoietin titer in response to hypoxia, anemia, or injection of cobalt; removal of other organs had no effect on erythropoietin production. The effect of nephrectomy was unrelated to the impairment of excretory function.³⁰ On the basis of these studies, the authors suggested that the kidneys are the major site of erythropoietin production.

This conclusion was supported by the studies of Naets et al., who showed that bilaterally nephrectomized dogs became anemic and the erythroid elements in their marrow disappeared. After injection of erythropoietin, the marrow and peripheral blood indices reverted to normal.⁴⁹ Kuratowska provided more direct evidence that the kidneys produce erythropoietin by showing that isolated rabbit kidneys perfused with hypoxic fluids secreted erythropoietin into the perfusate.³⁸ Failure to detect elevated erythropoietin levels in anemic patients with renal failure suggest that the kidneys are also the major site of erythropoietin production in man.^{1, 28, 32}

Although the kidneys are responsible for the majority of the body's erythropoietin production, numerous reports in rodents and man indicate that erythropoietin can be produced in extrarenal sites which have not yet been identified.^{16, 26, 27, 46, 47, 50, 51} Extrarenal erythropoietin has common antigenic determinants with that of renal origin, and is likely to be identical to it.²⁶ The production of extrarenal erythropoietin is also apparently regulated by the tissue oxygen supply relative to its demand, just as is the production of renal erythropoietin.²⁶ Extrarenal sites, however, produce much smaller amounts of erythropoietin at any given level of stimulation than do renal ones, and therefore these sites are unable to maintain a normal red cell mass in the absence of the kidneys.

The role of the kidney in erythropoietin production has been further delineated in a series of experiments performed by Gordon and co-workers.^{10, 11, 60} These investigators reported that the kidney produces an enzyme (the renal erythropoietic factor; REF) which converts a plasma globulin, probably of hepatic origin (erythropoietinogenin) into biologically active erythropoietin. They have further shown that both REF and erythrogin are antigenically distinct from erythropoietin. The exact site within the kidney which is responsible for erythropoietin or REF production is not known. The juxtaglomerular apparatus has been suggested by some investigators,³³ but has been shown to be an unlikely site by others.¹⁹ The inability of patients with renal failure to produce red cells in sufficient numbers to maintain a normal red cell mass results primarily from damage to the site of erythropoietin or REF production. As a result, the production of renal erythropoietin is either partially or completely abolished, and stimulation of erythropoiesis becomes dependent on erythropoietin produced in extrarenal sites. These sites, although regulated by the same stimuli as renal ones, are capable of producing only a fraction as much erythropoietin, and consequently the red cell mass is maintained at a subnormal level. When renal erythropoietin production is abolished completely, the red cell mass is maintained at so low a level that transfusions are required to prevent patients from developing symptoms of hypoxia.

In addition to this defect in erythropoietin production, inhibitors of erythropoiesis have been demonstrated in the kidneys and also in the plasma of patients with chronic renal disease.^{20, 37} Improvement in the blood count, the plasma iron clearance rate, and the rate of iron incorporation into new red blood cells²⁵ has been reported after dialysis of uremic patients,^{17, 39} and suggests that these inhibitors contribute significantly to the suppression of erythropoiesis which occurs in uremic patients.

Hemolysis of significant magnitude occurs in some patients with renal failure. This may result from at least two apparently different mechanisms. The first occurs primarily in those patients with disease of the small blood vessels.⁴ These microangiopathic lesions predispose towards deposition of fibrin along the damaged endothelium of small blood vessels. The fibrin strands impede the flow of red cells traversing these channels and cause damage to their membranes. Some cells are disrupted at the site of injury; other cells escape this obstacle in a damaged form, and may be characterized morphologically as schistocytes.^{5, 54} The rate of hemolysis is related to the amount of microangiopathy and to the number of schistocytes in the blood smear.⁴

The second type of hemolysis which occurs in patients with renal failure is caused by an abnormal plasma factor, present particularly in patients with rapidly progressive uremia, which is probably toxic to red cell metabolic processes.^{48, 58} "Burr" cells have been thought to constitute a morphologic abnormality produced by this same plasma factor. However, some studies indicate that the number of "burr" cells in the smear is related more to the degree of uremia than to the amount of hemolysis.^{55, 56} The nature of the plasma substance responsible for red cell damage is not known.

As a result of the frequent occurrence of uremic gastroenteritis and bleeding diathesis secondary to abnormal platelet function,⁴¹ patients with renal failure are particularly prone to gastrointestinal hemorrhage and iron deficiency anemia.^{1, 42}

Low serum iron levels may also occur in the presence of adequate or increased iron stores, suggesting that some patients with renal failure have a difficulty in mobilization of storage iron which is similar to the defect which has been demonstrated in patients with chronic inflammation or neoplasms.⁷

THERAPY OF THE ANEMIA OF RENAL FAILURE

The anemia of each individual with chronic renal disease should be carefully investigated to determine to what extent the various complicating factors described in the previous section contribute to it. Correction of treatable complications such as iron deficiency, folate deficiency, secondary infection, or reversible vascular disease will at times ameliorate the anemia sufficiently to obviate the need for transfusions. In severely uremic patients, improvement of the chemical composition of the plasma by dialysis increases the ability of the marrow to produce

red cells, and may markedly decrease the patient's transfusion requirements.¹⁷ Dialysis probably does this by removing inhibitors to erythropoiesis. Evidence that dialysis also increases red cell survival in patients with prominent hemolysis is more tenuous, but has not been definitely excluded.

Treatment of the more specific defect in erythropoiesis which results from insufficient erythropoietin production is at present unsatisfactory. Erythropoietin preparations suitable for human use are not yet available. Only cobalt³¹ and anabolic or androgenic steroids^{23, 44} are presently known to increase erythropoietin production. Cobalt is a toxic substance which probably acts to increase erythropoietin production by interfering with tissue oxygen utilization.^{2, 21} Accordingly, although it is capable of increasing the red cell mass of patients with renal damage,³⁴ it is questionable whether cobalt actually results in any net improvement of tissue oxygenation.

Anabolic and androgenic steroids increase erythropoiesis, at least in part, by sensitizing renal sites of erythropoietin production so that they produce more of the hormone in response to any given level of stimulation.²⁴ Several case reports suggest that the anemia of patients with renal failure may improve after treatment with androgens.^{14, 22} However, these patients had some remaining kidney tissue. Whether androgens will be useful in therapy of anephric patients or those with "end stage" kidneys remains to be demonstrated. Mirand et al.⁴⁵ did observe a small increase in the plasma erythropoietin level of one anephric patient treated with androgens. De Gowin et al.,¹⁴ however, observed no response to androgens in an anephric patient. Anephric rodents are stimulated to produce increased amounts of erythropoietin by exposure to hypoxia, anemia, and the injection of cobalt, but not by injection of androgens.²⁵ Therapy with anabolic or androgenic steroids has additional limitations, in that these agents tend to increase the plasma volume and consequently may be poorly tolerated by patients with heart disease. They also cause disfiguring hirsutism in females; 17-methyl compounds may cause serious damage to the liver. Accordingly, judicious use of blood transfusions remains the mainstay of therapy in patients with renal disease who become symptomatic because of severe anemia.

It is hoped that in the future this form of therapy will be replaced by the development of erythropoietin preparations suitable for human use; of substances capable of enhancing erythropoietin production by extra-renal sites; or of substances which increase the response of erythroid precursor cells to the small quantities of erythropoietin available to the marrow of patients with severe renal disease. Recent reports that some steroid compounds act directly on the bone marrow to stimulate erythropoiesis provide the prospect that they might prove useful in management of this refractory form of anemia.⁴⁰

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Management of Essential Hypertension

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The prevalence of high blood pressure is approximately 10 per cent in most populations. Over 20 million Americans are affected by high blood pressure, and it constitutes one of the major health problems in the United States. Although the etiology of primary, or essential, hypertension is not yet fully understood, much is known of the life history of the condition and its effects on the cardiovascular system. A brief 25 years ago very little was available to the physician in his efforts to intervene in the course of this disease. Today a number of potent drugs are at the clinician's disposal, and with these, singly or in combination, he is able to lower blood pressure in the great majority of cases. It is the purpose of this paper to discuss the rational basis for using these drugs and the practical technique of administering them in the office management of primary, uncomplicated hypertension.

Although a number of new causes for hypertension have been identified in recent years, most hypertension remains primary (essential) in nature. Because epidemiological studies have shown that blood pressure is a continuously distributed variable, roughly approximating the normal frequency curve, any cutoff point identifying a given value as high must be arbitrary. Nevertheless, actuarial data clearly show the increasing mortality ratio which can be assigned to relatively modest increases in either systolic or diastolic blood pressure.¹ Thus, men with casual blood pressures of 140 mm. Hg systolic and 90 mm. Hg diastolic have a 50 per cent increase in mortality over a 20 year period, compared to the expected incidence. There is an increase of over 100 per cent for values of 160 mm. Hg systolic and 100 mm. Hg diastolic.¹⁸

A number of long-term, prospective studies in the United States have all confirmed the relationship of hypertension to accelerated atherosclerosis and coronary artery disease.⁸ A similar relationship is known to exist for cerebrovascular disease.³⁰

If then, as it seems to be clearly evident, modest elevations in blood pressure are associated with accelerated atherosclerosis of the coronary and cerebral circulation and a significantly increased mortality rate,

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what is the evidence that lowering the blood pressure will alter the course of the untreated disease? The answer to this question must be considered not only from the standpoint of a hoped-for beneficial effect on a given end-point, but also, contrariwise, from the standpoint that treatment might exert a deleterious effect. Further, the drugs in question carry known side-effects, and, possibly, as yet unknown long-term hazards. Thus the physician must weigh all the available evidence before making his decision to treat each individual patient. The multiple aspects involved in the decision to treat patients have been well reviewed by Feinstein.⁹ Such an on-going critical appraisal of clinical judgment in cases of hypertension would seem to be especially appropriate.

Surprisingly, there is very little conclusive proof that treatment exerts a beneficial effect on the course of mild hypertension. A controlled, double-blind study of this question is now underway, but after more than 4 years no highly significant difference in morbidity between treated and placebo-treated groups has been shown.¹¹ Fries reasons that this may be so because atherosclerosis is a slowly developing process which requires a longer period of time to manifest a difference between treated and untreated groups.¹⁰

Some have argued that treatment in mild, uncomplicated hypertension is of no proven value.^{13, 14, 23} For moderate to severe hypertension, clear-cut evidence has recently been presented to support the value of treatment.^{7, 15, 29, 35} The results of treatment in patients with malignant hypertension are so well established,^{7, 15, 19, 29, 35} that withholding therapy cannot be justified.

In the final analysis, each patient must be considered individually, and a number of factors must be evaluated before a decision about therapy can be reached. In the following sections, a suggested procedure for such an evaluation is presented.

PRELIMINARY EVALUATION

The individual with high blood pressure of mild to moderate severity is often asymptomatic and totally unaware of his status. Hence, hypertension is usually found on routine examination. This fact is one of the most cogent arguments in favor of regular examinations of the clinically healthy individual.

Primary hypertension is uncommon in the first two decades of life, and is seen thereafter with increasing frequency until around age 50. There is a well-known familial incidence, and individuals from hypertensive families should be under special surveillance. Hypertension of sudden onset or hypertension developing after the age of 50 should raise doubts regarding its primary etiology, and a careful work-up to investigate possible underlying causes is warranted.

Blood pressure is often a labile phenomenon, and in the early stages of primary hypertension wide fluctuations may be seen. If, on repeated examinations, values above the upper limits of normal are seen, a diag-

nosis of hypertension can be made. As already pointed out, the cut-off point for the upper limit of normal is entirely arbitrary. The value of 140/90 mm. Hg would seem to be justified by actuarial data. The World Health Organization has set 160/95 mm. Hg as the cut-off point. Further division of those in the hypertensive range is equally arbitrary but serves some useful purpose in allowing comparison of various studies. The Veterans Administration Cooperative Study⁷ has used diastolic pressure alone as a criterion, and considers mild hypertension to be 90 to 114 mm. Hg, moderate hypertension, 115 to 129 mm. Hg, and severe hypertension, 130 mm. Hg and over.

In the initial evaluation of any hypertensive individual, the blood pressure should be measured on repeated occasions, with the patient lying, sitting, and standing, in order to establish a baseline for evaluating the effect of future treatment. During this phase, such simple therapeutic measures as mild sedation and weight reduction for obesity may be employed, but it is not to be expected that they will be adequate measures by themselves for control of significantly elevated blood pressure. Rigid salt restriction has been known to lower blood pressure, but the level of daily intake necessary to accomplish this is critical. Long-term adherence to such a diet is not feasible or practical. Modest salt restriction (no added salt in cooking or at the table) should be inherent in any regimen for blood pressure control. Patients with symptomatic or accelerated blood pressure (severe headaches, eye ground changes, cardiac or renal insufficiency) should be hospitalized for evaluation.

It is not within the scope of this presentation to discuss in detail the diagnostic studies required to identify the underlying causes of secondary hypertension. A high index of suspicion should be maintained, however, in those individuals under 20 years of age, those over 50 years of age, those without a family history of hypertension, and those in whom hypertension appears suddenly or worsens suddenly.

The following is suggested as a practical baseline diagnostic work-up for the hypertensive individual:

1. A careful history with emphasis on genitourinary tract infections, abnormalities in urinalyses, and date of onset of hypertension as determined by previous routine examination.

2. Complete physical examination with emphasis on funduscopy, bruits over major arteries and the abdomen, heart size, blood pressure in various positions in both arms and legs.

3. Chest x-ray for heart size.

4. Electrocardiogram.

5. Careful urinalysis. When the history of sediment suggests the possibility of pyelonephritis, culture of a clean-voided specimen is indicated.

6. Assessment of renal function. If the blood urea nitrogen is normal, and the random urine specific gravity is 1.020 or greater, renal function is considered normal. Endogenous creatinine clearance is an excellent method for quantifying renal function for baseline evaluation.

7. Serum electrolyte determinations: sodium, potassium, chloride, and carbon dioxide.

8. Rapid-sequence intravenous pyelography.

9. Plasma cholesterol and 2 hour postprandial blood sugar determinations.

Completion of these studies should effectively eliminate the likelihood of secondary hypertension in the majority of cases. It is then possible to make a decision regarding therapy. In cases of mild hypertension, some hesitation may be warranted if the individual is normal in every respect except for the presence of elevated blood pressure, for the decision to treat should have long-term implications. The unpleasant and harmful side-effects of drug therapy must be carefully weighed against the expectation of gain from lowering the blood pressure. The risk factor concept which has evolved for coronary atherosclerosis³⁰ is useful in reaching a decision regarding mildly hypertensive individuals. If other factors known to accelerate atherosclerosis are present, then vigorous treatment of even mild hypertension is mandatory. Of particular importance as risk factors are: cigarette smoking, hypercholesterolemia, hypertriglyceridemia, and diabetes.

INSTITUTION OF THERAPY

Therapy should be instituted with the mildest, best tolerated drug. In the hands of most investigators, oral diuretics have proven to be effective and well tolerated. While a number of modifications in the chemical structures of diuretics have been made, the various thiazides differ chiefly in their duration of action. Other diuretics such as chlorthalidone and furosemide appear to have similar modes of action and side effects.²⁴ Triamterene and ethacrynic acid are chemically distinct and have different pharmacological properties.

All these drugs enhance renal excretion of sodium in excess of water. The precise mechanism by which this occurs is not known, but it appears to be the result of inhibited sodium transport from the proximal tubular fluid. As a result of this diuretic action there is a decrease in blood volume, a reduction in cardiac output, and a fall in blood pressure. Vascular reactivity appears to be decreased, possibly as a result of depletion of sodium and water in the vascular wall.

Table 1. *Management of Primary Hypertension*

SEVERITY	BLOOD PRESSURE RANGE (MM. HG)	DRUG	DOSAGE
Mild	Systolic: 140-170 Diastolic: 90-114	Chlorothiazide	500-1000 mg./day
		Hydrochlorothiazide	50-100 mg./day
		Chlorthalidone	50-100 mg./day
		Bendroflumethiazide	5-20 mg./day
Moderate	Systolic: 150-200 Diastolic: 115-129	Diuretic <i>plus</i>	
		Reserpine <i>and</i>	0.1 mg. b.i.d.
		Methyldopa <i>or</i>	250-1000 mg. t.i.d.
		Hydralazine	25-100 mg. t.i.d.
Severe	Systolic: 180-250 Diastolic: $\geq$ 130	Diuretic <i>plus</i> guanethedine	10 mg./day or more as needed

Oral diuretics are especially valuable in the therapy of hypertension, because they are effective when the patient is in either the supine or the erect position. In order to minimize excessive reduction of the extracellular fluid, oral diuretics should be given in small doses, initially with step-wise increments at intervals of from 7 to 10 days. The dose response curve of chlorothiazide has been shown to be relatively flat,¹² and it is unlikely that further reductions in blood pressure can be expected by increasing the dosage beyond a point. Initial and maximal daily doses suggested for representative thiazides are as follows: chlorothiazide, 500 to 1000 mg.; hydrochlorothiazide, 25 to 100 mg.; bendroflumethiazide, 5 to 20 mg.; chlorthalidone, 50 to 100 mg. Successful lowering of blood pressure with diuretic therapy alone can be anticipated in about 50 to 75 per cent of patients. The therapeutic goal should be the consistent lowering of blood pressure to values below 140 mm. Hg systolic and 90 mm. Hg diastolic.

The major contraindications to therapy with diuretics are anuria, increasingly severe azotemia, and hepatic failure. Side-effects which do not prohibit their use are hyperglycemia, hypokalemia, and hyperuricemia.

Although the diuretics cause impaired glucose tolerance in the majority of subjects, fasting blood sugar is infrequently elevated and latent diabetes is rarely exacerbated. Preexisting diabetes may become worse. All these effects are reversible, and permanent diabetes has not been shown to be caused by the use of diuretics.²⁴

Hypokalemia is a frequent side-effect of diuretic therapy. Seen in about two thirds of patients, hypokalemia occurs as a result of kaluresis prolonged long after the decreased extracellular fluid volume and exchangeable sodium have returned to pretreatment levels. It is particularly likely to occur in patients on strict dietary restriction of sodium and is of greatest danger in patients concurrently on digitalis therapy. Dietary supplements of foods high in potassium (fruit juices and raw fruits) should be encouraged as tolerated. If serum potassium is not maintained, potassium salts in various liquid preparations are available. Enteric-coated potassium chloride has been associated with stenosing ulceration of the small bowel, and combinations of thiazides and potassium have been withdrawn from the market. At present, the best course of action would appear to be the simultaneous use of diuretics such as triamterene and spironolactone which are not associated with potassium loss. Spironolactone in a dose of 50 to 100 mg. daily has been reported to be equally as effective as hydrochlorothiazide in lowering blood pressure,³⁴ and the two in combination act in an additive fashion. Supplemental potassium should be used with caution under these circumstances. A side-effect of spironolactone is gynecomastia. This is reversed upon cessation of the drug.

Hyperuricemia is the third major side-effect of diuretic therapy. Ordinarily, non-gouty individuals with hyperuricemia remain entirely asymptomatic and require no treatment. In gouty subjects, however, acute attacks are common and require management with uricosuric agents. If this fails to control the clinical manifestations of gout, thiazide therapy may need to be discontinued and reliance placed on spironolactone alone.

COMBINED THERAPY

Although diuretic therapy alone will effectively control hypertension in the majority of cases, it will not do so in all cases and it is necessary to use combinations of two or more antihypertensive drugs under these circumstances. Recognizing the need for these combinations, the pharmaceutical industry has made over 50 available. Their use when therapy is initially begun is to be condemned, however, because it is not possible to adjust the dose of each component drug according to the individual's need.⁵ Once a satisfactory therapeutic regimen has been worked out, the advantage of a single tablet rather than two or three justifies the use of a comparable fixed combination if one is available.

A number of drugs are available as supplements to the basic diuretic regimen. Although most of these are more potent than the diuretics, their toxic side-effects are often more pronounced and less tolerable.¹² In a double-blind controlled comparison of various combinations of drugs, the combination of 500 mg. of chlorothiazide and 100 mg. of rauwolfia, twice a day, was superior to thiazide alone, thiazide and hydralazine, alpha-methyldopa alone, or thiazide and alpha methyl-dopa.^{27, 28} Hence, in those hypertensive patients who do not respond to diuretics alone, rauwolfia is the drug of choice to add to the regimen.

A variety of rauwolfia derivatives are available. All possess similar antihypertensive properties and side-effects. The main action of rauwolfia preparations is the depletion of catecholamine stores in the terminal postganglionic fibers, thus inhibiting neurotransmission. They also have a central action, of lesser importance, in releasing serotonin and other catecholamines from the vasomotor center in the brain. Since side-effects are unpleasant and are reached before an effective antihypertensive dose is achieved,¹² the rauwolfia preparations have a role in therapy only in combination with thiazides or other diuretics. Side-effects are seen in the majority of patients. Mental depression and nasal stuffiness are the most troublesome, but may be minimal and tolerable if the dosage is kept low.

Reserpine in a dose of 0.1 mg. twice a day is well tolerated and significantly potentiates the antihypertensive action of the diuretics.

If the blood pressure remains significantly elevated while the patient is receiving adequate doses of diuretics and rauwolfia, consideration should be given to adding a third drug to the regimen. Alpha-methyldopa, hydralazine, and pargyline have all been used in this manner.

Alpha-methyldopa inhibits decarboxylase activity, thereby interfering in the metabolic degradation of dopa to dopamine, a step in the formation of norepinephrine. It also inhibits the formation of serotonin. The precise way in which this known metabolic activity lowers blood pressure is still uncertain.^{3, 12} Alpha-methyldopa shares with the thiazide diuretics the ability to lower supine blood pressure. In the usual dose, it does not lower the glomerular filtration rate or renal blood flow, and therefore it is of particular value when renal function is impaired. It is given in divided doses of 250 mg. three times a day. If there is no response, the dose may be raised at intervals of no less than 2 or 3 days

to a maximum of 3.0 gm. a day. As with other antihypertensive drugs, there are undesirable side-effects such as drowsiness, lightheadedness, dry mouth, and gastrointestinal disturbances. These can generally be managed by reducing the dosage. More serious side-effects, requiring cessation of methyldopa, include acquired hemolytic anemia, development of a positive Coombs' test, granulocytopenia, or drug fever associated with hepatic dysfunction. Its use is contraindicated in patients with known hepatic dysfunction.

In place of alpha-methyldopa, hydralazine may be added to the basic regimen as a third drug. It appears to act chiefly on the peripheral arterioles, relaxing the smooth muscles of the walls.¹⁻³ It also stimulates the heart, increasing both the heart rate and stroke volume. In patients with preexisting coronary arteriosclerosis, angina may occasionally be produced or aggravated by hydralazine. A syndrome resembling lupus erythematosus has been described in patients receiving hydralazine, particularly in large doses. This can be avoided by limiting the dose of hydralazine to less than 300 mg. a day. Therapy should be instituted with small doses, 25 mg. three times a day, and increased to 50 mg. three times a day, if necessary, in several weeks. Although Pickering has found the therapeutic range to be too narrow to warrant its use,²⁵ the combination of thiazide, reserpine, and hydralazine was found to be effective in lowering the blood pressure in the vast majority of patients with moderate hypertension.⁷ Brest found it to be effective in approximately 80 per cent of hypertensive patients.²

Pargyline is the third of the drugs that may be added to the basic regimen of thiazide and rauwolfia. Although it inhibits the enzyme monamine oxidase, thereby increasing tissue stores of pressor amines, it appears to exert its antihypertensive action by the formation and accumulation of false neurotransmitters.³ As a result, peripheral vascular resistance is reduced by the decrease in sympathetic responsiveness. A complication of pargyline therapy which may limit its usefulness is the hypertensive crisis which can occur if large amounts of the pressor amine tyramine are consumed. Tyramine, present in certain cheeses, beer, and wine, is ordinarily degraded by monamine oxidase. Similar crises have also been seen with a number of other drugs, such as phenylephrine, meperidine, and various mood elevators. With adequate supervision, pargyline may be given in a dose of 20 to 50 mg. daily. Since pargyline is slow to act (and be excreted), the dosage should be raised slowly, at infrequent intervals. An orthostatic effect is seen, and erect as well as supine blood pressures should be measured.

SEVERE HYPERTENSION

Those patients with severe hypertension who fail to respond to combined therapy are candidates for treatment with guanethidine, the most potent antihypertensive drug now available. This drug should be given in addition to the basic diuretic management already discussed. The antihypertensive potency of guanethidine resembles that of the

Table 2. *Drug Effects*

	DIURETICS	RESERPINE	METHYLDOPA	HYDRALAZINE	GUANETHIDINE
Contraindications	Anuria Azotemia Hepatic failure	Use of guanethidine	Edema and heart failure Active hepatic disease	Coronary artery disease Rheumatic valvular disease	Use of reserpine or MAO inhibitors Pheochromocytoma
Major side effects	Hyperglycemia Hypokalemia Hyperuricemia	Depression Nasal congestion Aggravation of ulcer symptoms	Hemolytic anemia Granulocytopenia Drug fever	Lupus erythematosus syndrome	Orthostatic hypotension Diarrhea Bradycardia
Minor side effects	Anorexia Constipation Dizziness	Weight gain Nightmares	Drowsiness Vertigo Dry mouth	Headache Tachycardia Gastrointestinal disturbances	Inhibition of ejaculation Fatigue Edema

ganglionic blocking drugs but it has supplanted them in clinical use because of relative freedom from undesirable side-effects. Its anti-hypertensive action is seen chiefly when the patient is in the erect position.

Guanethidine acts by blocking the release of norepinephrine at the nerve endings and depleting the norepinephrine stores in the heart.²⁰ Venous tone is reduced and cardiac output falls, especially when the patient is in the upright position. Renal, cerebral, and coronary blood flow are all reduced. Hence, this drug must be used with great caution in patients with renal or cardiac insufficiency. Since the onset of action is slow, the drug should be introduced in a low dosage which is raised with caution every 3 to 5 days until the desired effect on standing blood pressure is achieved. The initial dose is 10 mg., and dosage may be increased in increments of 10 mg. as needed. The entire dose may be given once a day. Because of wide fluctuations in blood pressure, from excessively low values in the early morning to undesirably high values in the late afternoon, patients using guanethidine should be trained to determine their own blood pressure at home and at work. A record should be kept for evaluation at each office visit.

Guanethidine should not be used with pargyline, or in cases in which a pheochromocytoma is suspected. It should not be used in combination with rauwolfia. Side-effects include early morning weakness, orthostatic hypotension, and diarrhea. Other adverse effects include inhibition of ejaculation, fluid retention, and aggravation of asthma. Benthidine, which has a similar mode of action to that of guanethidine, may be preferable in that it exerts a maximal effect in about 4 hours and does not cause diarrhea. It has not been released for clinical use in the United States, however.

NEW DRUGS

Although there has been a marked reduction in the number of new drugs introduced for the treatment of hypertension in recent years, several have been advocated and are currently undergoing evaluation. Propranolol, which acts as a beta-adrenergic blocking agent, lowers blood pressure by reducing cardiac output. Its chief advantage is that it does not interfere with the ability of the vascular bed to respond with vasoconstriction when the patient assumes the erect position, exercises, or is in a hot environment. In a recent report, 84 per cent of 105 patients treated with propranolol achieved a diastolic value of 100 mm. Hg or less.²⁶ Debrisoquin, a postganglionic sympathetic blocking agent, is more effective in combination with other drugs and is well tolerated. It would appear to have limited utility, although its brief duration of action makes control of the orthostatic hypotension it produces easy to manage.²²

COMMENT

A number of potent drugs are available for the management of primary hypertension. These can be given in a logical, progressive fashion

with the realistic expectation that blood pressure can be significantly reduced to "normal" levels in the great majority of patients. There is wide consensus that therapy with these drugs should be instituted early and maintained on a long-term basis if accelerated atherosclerosis is to be prevented.^{10, 16} Several reports^{6, 32} have suggested that a very small percentage of patients successfully treated for several years may remain normotensive when therapy is stopped. There appears to be less likelihood of this outcome in patients with severe hypertension or in those with vascular complications.

Recent statistics have reported declines of 35.3 per cent in death due to strokes and of 63.1 per cent in death due to hypertensive heart disease since 1950 in individuals under the age of 65.²¹ This striking advance would seem at first glance to be creditable to the wide-spread effective use of the currently available drugs. Yet there is disquieting evidence that this is far from the true state of affairs.

Wilber,³³ in a random sampling of a Georgia community found that 42 per cent of those found to be hypertensive were unaware of their condition. Only 30 per cent of the hypertensive individuals were undergoing treatment. In only half of these, or 15 per cent of the total, was the blood pressure under good control. Within 3 months doctors had lost track of 56 per cent of patients who had been started on therapy. Using intensive follow-up by public health nurses, the percentage of those under good control was raised to 80 per cent. Within 2 years after this intensive effort had been terminated, only 29 per cent were still under good control. Wilber concluded that most patients are ignorant of the necessity of continuous follow-up and long-term treatment, and that the major reason for the failure to control high blood pressure is the failure of the patients to take medication. It was noteworthy that race, education, and social level were not important factors.

These findings are not unique to Georgia. In an industrial population in Chicago screened for susceptibility to coronary heart disease, 63.3 per cent of those individuals found to have elevated blood pressure were unaware that they had hypertension. Of those who gave a history of knowledge of the condition, only 56.2 per cent were receiving treatment at the time. In a poverty-stricken Chicago community, 47 per cent of women and 77 per cent of men found to be hypertensive on a door to door survey were unaware of the condition.¹⁷

The reason for the striking reduction in mortality due to strokes and hypertensive heart disease is, therefore, not clear. It may be that physicians are willing to institute and maintain therapy of severe hypertension which usually causes the vascular complications of stroke, hemorrhage, ruptured aneurysms, and heart failure. It would seem that they are less willing to approach milder degrees of hypertension in as aggressive a fashion. This would account for the fact that there has been no corresponding decrease in death due to coronary atherosclerosis in the period since 1950.

CONCLUSION

Primary hypertension can be successfully managed in the great majority of patients with the presently available drugs. Starting with

the mildest and safest drugs, the diuretics, additional drugs should be added to the therapeutic regimen as necessary to reduce the blood pressure to normal. Long term maintenance of therapy is essential. There is convincing evidence that therapy should be started early in the course of hypertensive disease, when the pressure is only mildly elevated.

ADDENDUM

Since submission of this paper, the results of the Veterans Administration Cooperative Study Group on Antihypertensive Agents have been published regarding treatment of patients with diastolic blood pressure averaging 90 through 114 mm. Hg (J.A.M.A., 213:1143, 1970). The risk of developing a morbid event was reduced over a 5 year period from 55 per cent to 18 per cent by treatment. The higher the pretreatment level of blood pressure, the greater was the benefit. Treatment was most effective in preventing hypertensive complications and least effective in preventing atherosclerotic complications.

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The Management of Hypertension Associated with Disorders of Function of the Endocrine Glands ("Endocrine Hypertension")

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As the clinical spectrum of hypertension emerges, a wide variety of hormonal disturbances are found to be associated with elevated blood pressure ("endocrine hypertension"). In some cases, the hormonal disorder is the direct cause of hypertension, as in the syndrome of excessive catecholamine secretion by chromaffin tumors. In other instances, a less direct etiologic relationship prevails; in yet others the association between hypertension and hormonal disturbances remains at the level of empirical observation.

This review will deal with a number of endocrine syndromes which have been found to occur frequently in association with hypertension (Table 1). Of greatest clinical importance are those involving excessive secretion of hormones of the adrenal medulla and adrenal cortex. Hypertension of adrenal origin may be severe and lethal yet, unlike most forms of hypertension, be entirely curable if recognized. Fortunately, considerable understanding of the pathogenesis of adrenal hypertension has evolved, and present concepts of management of the adrenal hypertensive syndromes, based on this understanding, will be presented in some

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Table 1. *Classification of Endocrine Syndromes Associated with Hypertension*

I. Pituitary gland
A. Anterior pituitary: acromegaly
B. Posterior pituitary: vasopressin intoxication
II. Parathyroid gland
A. Hyperparathyroidism
B. Hypercalcemia of nonparathyroid origin
III. Thyroid gland
A. Hyperthyroidism
B. Hypothyroidism
IV. Islets of Langerhans: diabetes mellitus
V. Adrenal medulla
A. Catecholamine-secreting tumors
1. Pheochromocytoma and pheochromoblastoma
2. Ganglioneuroma and neuroblastoma
B. Adrenal medullary hyperplasia
VI. Adrenal cortex ^c
A. Cushing's syndrome
B. Primary aldosteronism
C. Congenital adrenal hyperplasia

^cFor more detailed classification of the disorders of the adrenal cortex associated with hypertension, see Table 2.

detail. The association of hypertension with the remaining endocrine syndromes listed is less well understood, and the importance of this association, for the clinician, lies chiefly in his recognition of its existence. These syndromes will be discussed first, and briefly.

ACROMEGALY

The increased prevalence of hypertension in acromegaly is generally accepted, although statistical proof has not been easy to achieve.² The common occurrence of atherosclerosis and congestive heart failure in acromegaly probably both obscures the presence of hypertensive disease in some patients, and renders hypertension, when present, a greater threat. A report from the Mayo Clinic presented evidence suggesting that in patients with hypertension and active acromegaly, pituitary irradiation usually induced at least a temporary reduction of blood pressure.⁸¹ This report would have more convincingly demonstrated a relation between growth hormone excess and hypertension had the patients been shown to have a fall in growth hormone levels without impairment of secretion of other pituitary factors, such as ACTH, following irradiation. Nevertheless, the finding is of practical interest. The genesis of hypertension in acromegaly is unknown, and its treatment does not differ from that in other clinical settings.

VASOPRESSIN INTOXICATION

Inappropriate endogenous antidiuretic hormone (vasopressin) secretion, such as occurs in a variety of clinical disorders, including lung tumor, pulmonary infection, and intracranial lesions, has not been shown

to result in elevated blood pressure. This may seem surprising, since the standard bioassay for this hormone is based on its pressor effect in anesthetized animals. There are two explanations for this paradox. First, the dose of vasopressin required to produce marked vasoconstriction and elevated peripheral resistance is, in normal man, in excess of that producing maximal antidiuretic effect. Secondly, reflex bradycardia and fall in cardiac output ordinarily compensate for vasopressin-induced increase in peripheral resistance, resulting in small and transient changes in blood pressure. Thus, elevation in blood pressure subsequent to vasopressin administration in man requires large pharmacologic doses, or a patient with impaired autonomic reflexes, or both.^{21, 91} The management of vasopressin intoxication, obviously, lies in its prevention by avoiding excessive dosage in the treatment of diabetes insipidus, and by recognizing susceptible patients. These may include patients with autonomic insufficiency, on ganglionic blocking drugs, under anesthesia, or with central nervous system damage.

HYPERPARATHYROIDISM

Approximately a third of patients with hyperparathyroidism and hypercalcemia are found to be hypertensive.⁵² Renal disease from nephrocalcinosis and nephrolithiasis, a common result of sustained hypercalcemia of parathyroid or other origin, has generally been held to be the cause of this high prevalence of hypertension. Following successful treatment of hypercalcemia, both renal function and blood pressure may return partially or entirely to normal, this recovery presumably accompanying reversal of the renal lesion. Recently, however, it has been proposed that hypercalcemia may also have a direct effect on blood pressure, independent of renal damage, and fully reversible upon lowering of serum calcium.²⁰ Thiazide diuretics should be used with caution, if at all, in the treatment of hypertension in hyperparathyroid patients, since hypercalcemia provoked by chlorothiazide has been reported in such patients.⁷⁰

HYPERTHYROIDISM

Only systolic, not diastolic, hypertension is found with increased frequency in hyperthyroidism. Diastolic pressure is usually found to be normal or low, so that, characteristically, pulse pressure is wide. No clinical hazard is felt to attend this blood pressure pattern in itself, and no antihypertensive therapy is indicated. It is true, however, that adrenergic blockade with such drugs as guanethidine and propranolol, drugs used in treatment of hypertension, will in many instances diminish signs and symptoms of hyperthyroidism, including those related to increased cardiac output.⁷¹ With this form of therapy, systolic pressure and mean pressure may fall, but this fall must not be regarded as a primary therapeutic goal.

HYPOTHYROIDISM

The clinical observation that hypertension is unusually common in myxedematous patients has, as in the case of acromegaly, proved difficult to verify statistically. A report from the Mayo Clinic similar to the one regarding hypertension and acromegaly nevertheless provides information of clinical utility.²⁷ In this large series of hypertensive myxedematous patients, about a third were said to have had return of blood pressure to normal levels following thyroid hormone replacement, and another third showed some improvement of blood pressure. This finding suggests, at least, that treatment of mild or moderate hypertension in hypothyroid patients may often be deferred until full hormonal replacement is accomplished, with the frequent happy discovery that the hypertension has disappeared. The risk of producing angina in patients with coronary artery disease and hypertension by rapid thyroid hormone replacement must be kept in mind, of course. The physiologic basis for elevation of blood pressure in hypothyroidism is unknown.

DIABETES MELLITUS

Convincing evidence of increased prevalence of hypertension among diabetics is available, and, since diabetes is a common disorder, most physicians frequently encounter hypertensive diabetics. A number of theories to account for the association of these conditions, none fully satisfactory in itself, have been proposed.¹⁹ First, renal disease, often culminating in nephrogenic hypertension, is common in diabetics. In addition to the intercapillary glomerulosclerosis described by Kimmelstiel and Wilson, chronic pyelonephritis, necrotizing papillitis, and renal arterial and arteriolar sclerosis are well documented complications of diabetes. Secondly, diffuse diabetic microvascular disease has been suspected of increasing peripheral resistance and precipitating hypertension. And thirdly, excessive secretion of adrenal cortical steroids, short of the degree required to produce the full-blown syndrome of Cushing or Conn, might lead to concomitant hypertension and glucose intolerance. Regardless of the complexity of this clinical association, several points of practical utility may be made: (1) Prevention or effective management of urologic disease in diabetes may delay or prevent the development of severe renal and renal hypertensive disease. Unnecessary bladder catheterization is to be avoided, and acute urinary tract infections should be aggressively treated. Surgically correctible renal vascular disease is uncommon, but must not be overlooked as a possibility. (2) Weight gain, pregnancy, and administration of adrenal cortical steroids, all common clinical events, may precipitate or exacerbate both hypertension and diabetes in susceptible individuals. When glucose intolerance or hypertension appears in such a setting, the possibility of the other should be considered. The best remedy for both is removal, when possible, of the precipitating stress. (3) The thiazides, the drugs most widely used to treat hypertension, have the tendency to

elevate blood sugar and disturb diabetic control. Diazoxide, which has been used in hypertensive crisis, has the greatest hyperglycemic effect, but even chlorothiazide and hydrochlorothiazide should be used in diabetics only with awareness of this property.

PHEOCHROMOCYTOMA AND OTHER FORMS OF ADRENAL MEDULLARY HORMONE EXCESS

Catecholamine-secreting tumors are of several types. By far the most common type is pheochromocytoma, a tumor of adrenal medullary or accessory chromaffin tissue, which is usually but not always benign. Other neoplasms of neural crest origin, and therefore embryologically related to pheochromocytomas, may also secrete catecholamines and produce much the same clinical syndrome.⁴¹ These may be classified as ganglioneuroma (the benign form) and neuroblastoma (the malignant form). Functional tumors of this type are more commonly malignant. The histologic classification of individual tumors is occasionally in doubt; thus, in general, this discussion will deal with catecholamine-secreting tumors as a group, rather than "pheochromocytoma" alone. To complicate matters further, it is possible that adrenal medullary hyperplasia may exist as a separate physiologic entity producing a syndrome similar to that of neoplastic catecholamine secretion,⁶⁴ and that certain carcinoid tumors may be capable of secreting catecholamines, though the clinical significance of this is unknown.⁹⁰

The syndrome of excessive catecholamine secretion is so dramatic, and the cure potentially so satisfying, that it has received attention far out of proportion to its prevalence. Less than one per cent of hypertensive patients have catecholamine secreting neoplasms, but the condition has been frequently reviewed^{30, 35, 80} and most physicians have some acquaintance with the classical syndrome. It is common practice to separate patients with catecholamine excess into those with *paroxysmal* symptoms, especially headache, sweating, pallor, and anxiety, associated with marked hypertension, from those in whom hypertension is *persistent*, and may or may not be accompanied by these symptoms. In addition to these two forms, there are patients who display little or no hypertension, whose complaints may be minimal and may include abdominal pain, nausea, emotional disorders, symptoms of glucose intolerance, postural hypotension, or even episodes of profound *hypotension* unrelated to posture. Also, there are patients with paroxysms of hypertension and autonomic phenomena very like those caused by catecholamine-secreting tumors, yet without such tumors. Such patients are believed to have seizure activity involving the diencephalic autonomic regulatory centers. The problem of diagnosis remains considerable, but fortunately the widespread awareness of the syndrome of catecholamine excess and improvement in diagnostic methods combine to make early diagnosis frequently feasible.

Furthermore, improved understanding of the physiologic principles involved may be applied to decisions in management once the diagnosis

is suspected. A reasonable series of questions to be answered in approaching this problem might be:

1. Is a catecholamine-secreting tumor present?

The best tool for diagnosis of this condition, when suspected, is still measurement of urinary excretion of epinephrine, norepinephrine, or their breakdown products (Fig. 1). The assays most widely available are: (a) total urinary catecholamines (epinephrine plus norepinephrine), (b) urinary metanephrine plus normetanephrine (MN plus NMN), and (c) urinary vanillylmandelic acid (VMA). It is said that any one of these assays, properly performed, will detect over 90 per cent of cases of pheochromocytoma. Of the assays, that for VMA is most widely used, but if not properly executed, it is susceptible to false positive reactions due to dietary substances in certain foodstuffs such as vanilla and bananas. The assay for catecholamines is difficult to perform and not widely available. The metanephrine-normetanephrine assay is relatively easy, quite adequate, and may in the future become more popular. When the diagnosis is strongly suspected but the above assays are normal, urine should, if possible, be collected during the period immediately following a paroxysm, when transiently elevated values may be found.

If diagnosis remains in doubt, one of the pharmacologic provocative tests may be considered. Many have been devised, the best known being the histamine test,⁷⁴ the tyramine test,²⁴ and the phentolamine test. The first two involve drug-induced catecholamine release, resulting in rise of blood pressure; the latter, blockade of alpha-adrenergic receptors, producing a fall in blood pressure when excess catecholamines are present. All these tests carry definite risk of severe hypertension or hypotension, and are indicated only rarely. Perhaps the best use of the provocative tests is to induce a diagnostic rise in catecholamine excretion in difficult cases.

In relation to diagnosis of catecholamine-secreting tumor, it must be mentioned that several familial conditions are known to be associated with these tumors. Pheochromocytoma alone is at times a familial ill-

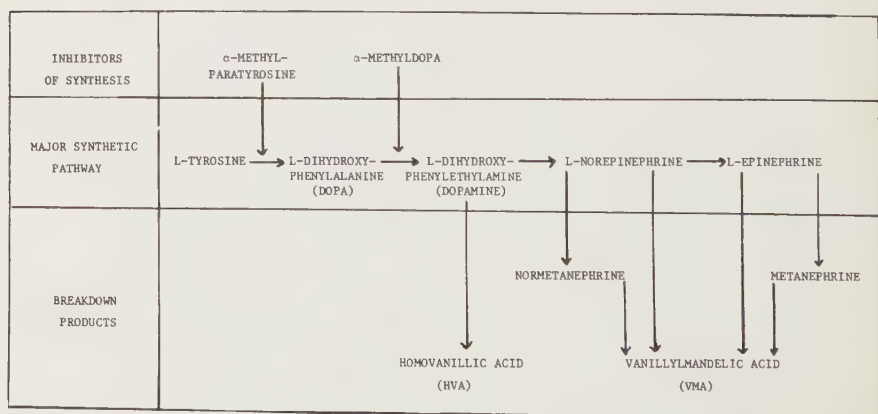


Figure 1. Simplified scheme of metabolism of catecholamines.

ness. The neurocutaneous syndromes, certainly von Recklinghausen's neurofibromatosis and von Hippel-Lindau disease, and possibly Sturge-Weber syndrome and tuberous sclerosis, are often associated with catecholamine-secreting tumors.³² The same is true of medullary carcinoma of the thyroid, which has been linked with pheochromocytoma and parathyroid adenoma as "Multiple Endocrine Neoplasia Type 2."³⁴ Any patient with one of these conditions, or with a relative with one, is at greatly increased risk to develop a catecholamine-secreting tumor.

2. What substance does the tumor secrete?

Knowledge of the spectrum of substances secreted by the tumor is of definite benefit in guiding pharmacotherapy, determining the tumor's location, estimating its size, and anticipating malignancy. Chemical determinations are essential to define the spectrum of compounds secreted, of course, but in some cases the clinical history will yield useful clues.

GUIDANCE OF PHARMACOTHERAPY. Nearly all patients with catecholamine excess require alpha-adrenergic blockade as the basic medical therapy, but there is often debate as to whether beta-blockade is also indicated. Patients who have hypotension and abdominal symptoms as prominent clinical features are commonly found to excrete unusually large quantities of epinephrine and metanephrine.⁶⁹ When this clinical and laboratory pattern is present, omission of beta-adrenergic blockade may be dangerous.

DETERMINATION OF TUMOR LOCATION. The enzyme converting norepinephrine to epinephrine is normally found only in adrenal medullary tissue and the organ of Zuckerkandl. Thus, it is not surprising that, with rare exceptions, neoplasms secreting large quantities of epinephrine arise from these sites. The converse is not always true, however; patients with high norepinephrine-epinephrine and normetanephrine-metanephrine ratios *may* have tumors arising from adrenal tissue.

ESTIMATION OF TUMOR SIZE. Many secretory tumors appear to store and degrade large quantities of catecholamine, releasing relatively little active substance into the circulation. When this is the case, the tumor may cause few symptoms, and grow to considerable size before coming to clinical attention. Tumors storing and degrading little of what they produce, on the other hand, are often accompanied by severe, constant, and rapidly progressive symptoms, discovered early, and found at surgery to be small. A high ratio of urinary catecholamines to VMA and a fulminant clinical course, therefore, suggest the presence of a rather small and possibly hard to locate neoplasm.¹⁸

ANTICIPATION OF MALIGNANCY. Some tumors secrete catecholamine precursors in addition to catecholamines and their breakdown products. The most important of these precursors are dopa (dihydroxy-phenylalanine) and dopamine (dihydroxy-phenylethylamine), which are most easily detected by analysis of urine for homovanillic acid, a breakdown product of dopamine (Fig. 1). Experience shows that many patients with elevated homovanillic acid excretion prove to have malignant tumors, some of them neuroblastomas.⁹¹ This finding is especially valu-

able, since histologic distinction of benign from malignant catecholamine-secreting tumors is difficult.

3. Where is the tumor?

Conveniently, most catecholamine-secreting tumors are located in or adjacent to the adrenal glands, and the vast majority are within the abdominal cavity. The remaining tumors may be found in the neck, mediastinum, or pelvis. Often the history gives valuable clues to the site of the tumor. Systemic symptoms following bending, coughing, sneezing, or straining at stool may occur when an intra-abdominal tumor is present. Symptoms following urination are described in patients with secretory tumors in the bladder wall, and cervical tumors may produce symptoms upon sudden movement of the head. Occasionally the lesion is palpable on physical examination. In these cases, and even in some in which the tumor is not palpable, pressure in the region of the tumor may elicit a paroxysm.

A wide variety of diagnostic procedures for localizing the tumor have been used, including retroperitoneal air insufflation, adrenal venography, vena-cavography, adrenal arteriography, aortography, and analysis of venous blood from various sites for catecholamine content.⁷³ All these maneuvers may be tolerated poorly by patients with catecholamine-producing tumors, and may carry considerable risk. Intravenous pyelography with nephrotomography remains one of the most informative and certainly the safest diagnostic study, and is indicated in most cases. Adequate adrenergic blockade is mandatory prior to any major procedure. Selection of the procedure or procedures to be used depends in part upon local experience and preference, but in every case requires careful clinical judgment of potential risks against potential gains.

4. What treatment is required?

The definitive treatment of catecholamine-secreting tumors is surgical excision. Medical therapy has three roles: preparation for surgery, management of unresectable malignant lesions, and treatment of patients with medical contraindications to surgery. For all these purposes, two types of drugs are of benefit. Most important at present are the adrenergic blocking drugs which are competitive pharmacologic antagonists of the catecholamines.^{16, 72} The major alpha-adrenergic blocking agents are phenoxybenzamine (Dibenzyline), which has sustained action, and phentolamine (Regitine), the effect of which is more transient. The prototype beta-adrenergic blocking drug is propranolol (Inderal). Alpha-adrenergic blockade is generally the most essential part of clinical control of catecholamine excess, lowering the blood pressure and preventing hypertensive paroxysms. Beta-adrenergic blockade is in some cases required to control cardiac arrhythmias and hypotension, which occur especially with substantial epinephrine secretion. It is suggested that adequate adrenergic blockade be achieved for 10 to 14 days prior to surgery, and even longer in some cases.⁸⁰ Several theoretical benefits result from this prolonged preparation, including re-establishment of normal blood volume in cases where contracted volume occurs, and

reversal of some metabolic effects of catecholamines, possibly including the metabolic cardiomyopathy.

Drugs blocking catecholamine synthesis (Fig. 1) form the other category of drugs useful for this condition. Alpha-methyl-dopa (Aldomet), which to some extent blocks the conversion of dopa to dopamine, has unfortunately proved inadequate for this purpose. Alpha-methyl-para-tyrosine,²³ a drug not yet widely available which blocks dopa formation from tyrosine, appears far more effective, and may in the future come into general use.

When surgery is planned, and medical preparation has been instituted, several preparatory measures remain. A strategy conference between the internist, anesthesiologist, and surgeon is highly desirable, since catastrophe strikes swiftly in these patients, and intraoperative eventualities must be foreseen by all involved. Equipment should be prepared for continuous monitoring of electrocardiograph and arterial and central venous pressures during surgery. Whole blood or other plasma volume expanders should be on hand in the operating suite, as should propranolol, phentolamine, norepinephrine, isoproterenol, and lidocaine, ready for immediate use. These measures may seem trivial, but in practice they are essential and easily overlooked.

Choice of anesthetic is difficult, since a fully satisfactory anesthetic method for this situation is yet to be demonstrated convincingly. Fluothane (Halothane) has been widely used,⁸⁰ but seems to sensitize the myocardium to the effects of catecholamines. Methoxyflurane¹⁷ and fluroxene³⁶ have been advocated recently, on the basis that they have less myocardial sensitizing effect, but experience with these agents is still limited. Agents provoking sympathetic discharge, including ether, cyclopropane, and possibly d-tubocurarine, are to be avoided, and it is possible atropine may increase the hazard of catecholamine-induced arrhythmias.

The major operative crises are usually hypertension or arrhythmia following manipulation of the tumor, or serious hypotension following its removal. At the time of interruption of venous drainage of the tumor, transfusion of large quantities of blood or other colloid, in excess of operative losses, is often necessary, and usually sufficient, to maintain blood pressure.⁸⁰ Lack of fall of blood pressure at this moment may indicate presence of additional functioning tumor tissue. Norepinephrine infusion may be necessary for a time postoperatively to sustain blood pressure, but, if volume replacement is adequate, not very frequently. Thorough surgical exploration of the entire abdominal cavity for additional tumors is indicated even when radiologic search has revealed but one mass, since these tumors are frequently multiple, especially in children. Undetected tumors or metastases may manifest themselves postoperatively by persistent elevation of urinary catecholamine or catecholamine metabolite levels.

DISORDERS OF FUNCTION OF THE ADRENAL CORTEX

Among disorders of endocrine glands accompanied by arterial hypertension, those affecting the adrenal cortex play a most prominent

role. Moreover, ever since Goldblatt demonstrated that experimental hypertension produced by clamping of renal artery³³ cannot be maintained in the absence of the adrenal cortex (or a proper substitution of adrenocortical hormones), adrenocortical secretion has been implicated also as a *sine qua non* in the production of hypertension other than that in which primary disturbance of hormonal function can be demonstrated: renal and "essential."⁴⁵ Although in these two types of hypertension, and particularly in essential hypertension, the exact relationship of adrenocortical secretion to the mechanism of increased arteriolar resistance, and consequent arterial hypertension, has not yet been elucidated, it is appropriate to mention that changes in the peripheral metabolism or secretion pattern of steroid hormones, or both, have been found in patients with essential hypertension. Whereas Touchstone et al.⁸⁷ demonstrated an increased *in vitro* production of 20-dihydrocortisols (11 β , 17 α , 20 α , 21-tetrahydroxypregn-4-en-3-one and its 20 β -epimer) by the adrenals of patients with essential hypertension, findings of Kornel and co-workers⁴⁷⁻⁵⁰ pointed to a decreased activity of steroid Δ^1 -hydrogenase, and increased formation rate of 6 β -hydroxycortisol (and its sulfate conjugate) and other polar cortisol metabolites. Furthermore, a *decreased* response in the aldosterone secretion to stimuli which normally elevate aldosterone levels, in spite of an appropriate increase in plasma renin and angiotensin levels has been found in patients with essential hypertension.⁹⁵ Whether these changes have a direct bearing upon etiology of essential hypertension, and if so, by which mechanism they would contribute to it, is still unknown.

An *increased secretion* of adrenocortical steroids has been demonstrated to be the causative factor of hypertension associated with *primary* dysfunctional disorders of the adrenal cortex. A proper diagnosis of these disorders, followed by the institution of a proper therapy is of utmost importance, since these are "curable" forms of hypertension.

Table 2 lists various disorders of the adrenal cortex invariably accompanied by hypertension.

DISORDERS RESULTING FROM A CHRONIC INCREASE IN THE PRODUCTION OF GLUCOCORTICOIDS

Cushing's Syndrome

All signs and symptoms in this disorder are the expression of metabolic abnormalities resulting from chronic hypercortisolemia. The increase in the production rate of cortisol results either from adrenocortical hyperplasia or from autonomously functioning adrenocortical tumor. Hyperplasia ensues in response to an increased production of adrenocorticotrophic hormone (ACTH). This may be due to: (1) an "*over-active*" *pituitary* (no sellar enlargement) due to an enhanced production of corticotrophin releasing factor (CRF), which is in turn probably the result of an increased output of neurogenic stimuli originating from diencephalon ("diencephalic syndrome") or cerebral cortex or both;

Table 2. Disorders of Function of the Adrenal Cortex Associated with Hypertension

DISORDER	STEROIDS PRODUCED IN EXCESS RESPONSIBLE FOR CLINICAL SYNDROME	STEROID RESPONSIBLE FOR HYPERTENSION	BASIC METABOLIC ABNORMALITY LEADING TO HYPERTENSION	TREATMENT
<i>Cushing's syndrome</i>				
A. Adrenocortical hyperplasia				
1. "Overactive" pituitary	cortisol	cortisol (?) and/or as yet unidentified steroid	unknown (sodium retention?)	Surgical: Bilateral adrenalectomy or pituitary irradiation Medical: o,p'DDD, aminoglutethimide, aminoglutethimide + Metopirone
2. Basophilic adenoma	cortisol			Surgical: Removal of adenoma Surgical: Removal of tumor
3. Chromophobe adenoma	cortisol			Surgical: Removal of adenoma Surgical: Removal of tumor
4. Ectopic ACTH-secreting tumor (lung carcinoma, pancreatic tumor, thymoma, carcinoma of ileum, medullary thyroid carcinoma)	cortisol			Medical: o,p'DDD, aminoglutethimide
B. Adenoma of adrenal cortex	cortisol and adrenal androgens			
C. Carcinoma of adrenal cortex	aldosterone			
<i>Primary aldosteronism</i>				
A. Adenoma of adrenal cortex (Conn's syndrome)	aldosterone			Surgical: Removal of adenoma and/or unilateral adrenalectomy
B. Bilateral hyperplasia	aldosterone			Medical: Cortisol or analogues
1. Glucocorticoid-remediable aldosteronism	aldosterone	aldosterone	sodium retention	Surgical: Partial adrenalectomy
2. Glucocorticoid-resistant aldosteronism	aldosterone, cortisol and adrenal androgens			Surgical: Removal of tumor
C. Carcinoma of adrenal cortex				

Table 2. Disorders of Function of the Adrenal Cortex Associated with Hypertension (Continued)

DISORDER	STEROIDS		BASIC METABOLIC ABNORMALITY LEADING TO HYPERTENSION	TREATMENT
	PRODUCED IN EXCESS RESPON- SIBLE FOR CLINICAL SYNDROME	STEROID RESPON- SIBLE FOR HYPERTENSION		
<i>Hypercorticism</i>				
A. Corticosterone-producing tumor of adrenal cortex	corticosterone	corticosterone	sodium retention	Surgical: Removal of tumor
B. Congenital adrenal hyperplasia (see below)				
<i>Congenital adrenal hyperplasia</i>				
A. 11β-hydroxylase deficiency	adrenal andro- gens DOC, S _R DOC, cortico- sterone	DOC	sodium retention	Medical: ACTH suppression with cortisol or analogues
B. 17α-hydroxylase deficiency		DOC (cortico- sterone?)	sodium retention	Medical: ACTH suppression with cortisol or analogues

(2) a *basophilic adenoma* of the pituitary (these adenomas are usually small in size and do not cause a radiologically recognizable enlargement of the sella turcica); (3) a *chromophobe adenoma* (secretion of ACTH by a chromophobe adenoma has been recognized only recently); this is usually big enough to cause sellar enlargement or visual disturbance (pressure on optic chiasm); (4) a so-called "*ectopic endocrine tumor*," that is, a tumor, usually malignant, originating from nonendocrine tissues (oat-cell pulmonary carcinoma, bronchogenic adenoma or carcinoma, pancreatic tumors, carcinoma of the ileum, thymomas, and medullary carcinoma of the thyroid) and producing ACTH-like or CRF-like substances.^{54, 62, 89} A nonhyperplastic hyperadrenocorticism may result from either adrenocortical adenoma, or carcinoma of the adrenal cortex. A rare instance of an ectopic adrenocortical tumor has been also reported.⁶⁵ Cushing's syndrome has been also described due to a mixed corticomedullary adenoma⁵⁹ and due to pheochromocytoma of the adrenal medulla secreting ACTH (ectopic ACTH-producing tumor).⁶⁸

The diagnosis of Cushing's syndrome is based on the typical clinical picture (not always, however, present)⁴⁶ and on laboratory findings pointing to the increased output of cortisol by the adrenal cortex. These consist of: lack of so-called diurnal (or, rather, circadian) variation in plasma levels of cortisol, lack of normal suppressibility of cortisol production with dexamethasone, increased urinary output of *free* cortisol⁶⁰ (urinary excretion of 17-hydroxycorticosteroids [17-OHCS], cortisol metabolites consisting mainly of *conjugated* corticosteroids, is not infrequently within normal range in Cushing's syndrome), and demonstration of an increased cortisol secretion rate by its direct measurement. An important adjunct in the diagnosis of Cushing's syndrome is radiologic demonstration of either tumor or hyperplasia of the adrenal cortex by adrenal venography or angiography or both.²²

Differentiation between hyperplasia and autonomous tumor of the adrenal cortex is accomplished by means of dexamethasone, metyrapone, and lysine-vasopressin tests,^{4, 34, 53, 66, 94} although equivocal or paradoxical results are to be occasionally expected.⁴² Hyperplasia due to ectopic ACTH-producing tumor is usually unresponsive to ACTH-suppression tests (dexamethasone), but puzzling exceptions have been reported.⁶⁷ It may be that in such cases the tumor was secreting CRF.⁸⁹

Since hypertension is almost invariably associated with Cushing's syndrome, regardless of its cause, its origin must be related to the increase in adrenocortical secretion or metabolic abnormalities resulting from it. With regard to any particular steroid being responsible for the creation of hypertension, no definite evidence points to cortisol, although chronic administration of pharmacologic doses of cortisol will result in sodium retention and hypertension. An increase in the production rate of certain polar metabolites of cortisol has been demonstrated to exist in Cushing's syndrome,^{29, 46} and it is quite possible that these steroids are directly produced by the adrenal cortex. However, it remains to be seen whether they have any relationship to the mechanism of hypertension in Cushing's syndrome. Thus, treatment of hypertension

in Cushing's syndrome is tantamount to the treatment of the whole disorder as such, and will depend on the pathogenetic mechanism.

In Cushing's disease caused by adrenocortical hyperplasia due to an "overactive" pituitary or basophilic adenoma (in both of which there is usually lack of radiological evidence of enlargement of the sella turcica), the treatment of choice is surgical: bilateral adrenalectomy with a proper steroid substitution therapy. However, equally good results have been obtained with irradiation of the pituitary with heavy (α , helium ions) particles. Less consistently positive results are obtained by implantation of radionuclides in the pituitary fossa.

More recently, medical management of Cushing's disease has been advocated with compounds found to possess "adrenocorticolytic" activity, 2,2 bis (2-chlorophenyl-4-chlorophenyl)-1,1-dichloroethane (o,p'DDD) and aminoglutethimide (Elipten), but the efficacy of this treatment awaits further evaluation.^{79, 86} Lately, a complete remission has been reported in patients treated with a combination of aminoglutethimide and metyrapone, the former blocking earlier stages of cortisol synthesis, the latter, 11β -hydroxylation.³⁷

If sellar enlargement is demonstrable in Cushing's syndrome, a chromophobe adenoma can be usually found; its removal results in the cure of the disease.⁵⁷ Adrenocortical hyperplasia due to ectopic ACTH (or ACTH + CRF)-producing tumor is properly treated by surgical removal of the tumor.⁵⁵

In cases of autonomous tumors of the adrenal cortex, the treatment of the adenoma is surgical removal of the tumor; that of carcinoma is surgical, medical or both, with o,p'DDD and/or aminoglutethimide.^{3, 79} In carcinoma, a frequent finding along with hypercortisolemia is a highly increased production of adrenal androgens, with resulting virilization in females or, in children, precocious puberty. The hyperandrogenism is not related to hypertension.

DISORDERS RESULTING FROM A CHRONIC INCREASE IN THE PRODUCTION OF MINERALOCORTICIDS

Primary Aldosteronism (Conn's Syndrome)

This is the most common cause of "endocrine" hypertension, and its recognition is of utmost importance particularly because it may masquerade as a clinical picture typical of essential hypertension.¹⁴

All signs and symptoms in this disease, including hypertension, are a direct result of a chronic hyperaldosteronemia. The increased production of aldosterone may be due to: (1) an aldosterone-producing adenoma (APA) of the adrenal cortex, which is most common;^{10, 12} (2) rare bilateral adrenocortical hyperplasia, involving mostly the zona glomerulosa;^{12, 31} and (3) very rarely, carcinoma of the adrenal cortex, producing aldosterone along with other steroids.¹

Since increased production of aldosterone is characteristic also of disorders associated with so-called *secondary* aldosteronism, it is of utmost importance to differentiate one from the other. Secondary al-

dosteronism is encountered in any disorder resulting in an increased stimulus to the renal juxtaglomerular apparatus leading to an increased secretion of renin and, consequently, to an increased production of angiotensin. It occurs in renal artery stenosis, in diseases of renal parenchyma associated with a decrease in renal plasma flow, and in renovascular hypertension (including "malignant hypertension"). It also appears in those nonrenal disorders, where there is a substantial decrease in the effective circulating plasma volume (ECPV): these include congestive heart failure, liver cirrhosis associated with hypoalbuminemia and ascites, and edematous states of various origin.²⁸ However, in these conditions hypertension is not present. Hypertension is also absent in the so-called Bartter's syndrome, in which hyperaldosteronism is a result of juxtaglomerular hyperplasia of unknown origin.⁹

The underlying mechanism of hypertension in primary aldosteronism, regardless of its cause, is sodium retention. However, the hyperaldosteronism of *secondary* aldosteronism, although responsible for certain electrolyte abnormalities generally associated with aldosterone excess, is *not* per se the cause of hypertension in patients with secondary aldosteronism. Consequently, elimination of the excess of aldosterone either by adrenalectomy (or removal of aldosterone-producing adenoma of the adrenal cortex) or by pharmacologic blockade with spironolactone will correct both hypertension and metabolic abnormalities only in primary aldosteronism. In secondary aldosteronism with hypertension, elimination of aldosterone excess results in the reversal of the metabolic abnormalities but does not relieve the hypertension. Thus, a high-dosage (400 mg. per day) long-term (3 to 5 weeks) spironolactone test has been used to predict the response that might be expected after adrenal surgery.⁸²

Differentiation of primary from secondary aldosteronism in hypertensive disease is best performed by measuring plasma renin activity (PRA), as suggested by Conn et al.¹¹ Plasma renin activity in patients with primary aldosteronism is undetectable; in secondary aldosteronism it is higher than in normal subjects. These differences are still greatly accentuated when potent stimuli for the secretion of renin are applied: a low-sodium diet (10 mEq. per day) for several days, and an upright position for a period of at least 4 hours prior to the test. Patients with primary aldosteronism fail to respond to these stimuli, their plasma renin activity remaining suppressed; those with secondary aldosteronism show a drastic increase in plasma renin levels.

Suppressed plasma renin activity is also found in a sizable portion (one fourth) of patients with essential hypertension.³⁸ Whereas the pathogenetic mechanism of this finding is not yet understood, these patients do not exhibit increased urinary excretion of aldosterone, nor is their secretion rate of aldosterone abnormally elevated.³⁹ Thus, a combination of aldosterone overproduction and subnormal plasma renin activity, unresponsive to stimuli which elevate this activity in normal people, is diagnostic of primary aldosteronism, whether hypokalemia is present or not.¹⁵

A test dose of angiotensin produces a far greater pressor effect in patients with either essential hypertension or primary aldosteronism

than it does in patients with renovascular hypertension (and secondary aldosteronism).⁴⁰ Although not entirely devoid of hazard, it may be cautiously used to help distinguish between primary from secondary aldosteronism in a hypertensive patient with *hypokalemia*. However, the test is of no value in distinguishing essential hypertension from primary aldosteronism with *normokalemia*.

A confirmatory test for aldosterone-producing adenoma is afforded by the aldosterone suppression test with desoxycorticosterone acetate (DOCA), described by Biglieri et al.⁶ With a high sodium intake, DOCA is administered for 3 days and aldosterone excretion is measured just before and on the third day. Failure to reduce urinary aldosterone levels into the normal range (or to depress normal levels) is significant, and is an indication for surgical exploration.

The majority of patients with essential hypertension respond to stimuli for increased renin-angiotensin production, such as severe sodium restriction, with a rise in plasma renin and angiotensin but *not* in aldosterone secretion.⁹⁵ The underlying mechanism of this dichotomy is unknown, but this finding offers means for distinguishing renovascular hypertension (with secondary aldosteronism) from essential hypertension in a hypertensive *normokalemic* patient. It also opens new avenues in the search for a causative factor in essential hypertension.

The autonomy of aldosterone-producing adenoma can be tested in still another way, as described by Espiner et al.²⁵ Under conditions of prolonged sodium restriction, physiological saline is infused on two consecutive days, and aldosterone secretion is measured before and during the second day of infusion. Patients with primary aldosteronism due to adenoma fail to suppress aldosterone production, whereas this is drastically reduced by sodium load in normal subjects. A similar effect is elicited by a high-sodium diet.¹⁴

An important adjunct to the diagnosis of aldosterone-producing adenoma, permitting localization of the tumor, is percutaneous trans-femoral bilateral adrenal vein catheterization with the estimation of aldosterone content in the right and left adrenal vein blood.⁶¹ An increased concentration of aldosterone confirms the presence, and establishes the localization, of a unilateral aldosterone-producing adenoma. Combined adrenal arteriography and venography may also aid in a radiological demonstration of a sizable adenoma or carcinoma of the adrenal gland,²² although this technique seems to have more value in determining the cause of Cushing's syndrome. Aldosterone-producing adenomas are frequently very small,¹⁴ as is the extent of adrenal hyperplasia in non-tumorous primary aldosteronism.¹²

Primary aldosteronism due to adrenocortical *hyperplasia* has been described.^{31, 51, 85} The factor responsible for the hyperplasia is unknown, and only a few patients with this disorder have been reported. Although the triad of suppressed renin activity, overproduction of aldosterone, and hypertension is the same as in primary aldosteronism due to aldosterone-producing adenoma, apparently some patients with hyperplasia respond to glucocorticoid (cortisol or dexamethasone) administration with a reduction in aldosterone excretion and hypertension, while others

do not. On this basis, non-tumorous primary aldosteronism has been subdivided by Laidlaw and associates^{75, 76} into two types: "glucocorticoid-remediable" and "glucocorticoid-resistant" aldosteronism.

Finally, adrenocortical carcinoma, a very rare cause of primary aldosteronism, has been also reported.¹ These patients differ from those with aldosterone-producing adenoma by exhibiting a simultaneous increase in the production of both glucocorticoids and adrenal androgens, although characteristically they present little clinical evidence of hypercortisolism or hyperandrogenism. Suppressed plasma renin activity, hyperaldosteronism, and hypertension are invariably present.

Cases of aldosteronism due to carcinoma of nonendocrine organs (bronchogenic carcinoma, carcinoma of the prostate) metastasizing to the adrenal cortex have been also reported.^{43, 58, 83} Whether the metastases actually produced aldosterone, or the parent tumor produced angiotensin-like peptides stimulating aldosterone secretion, remains to be determined.

Findings similar to those of primary aldosteronism can be produced by increased secretion of desoxycorticosterone (DOC) and corticosterone (B).⁷ These rare syndromes and their differentiation from primary aldosteronism are discussed on the following pages.

Treatment of primary aldosteronism depends on the pathogenetic mechanism leading to overproduction of aldosterone, sodium retention, and hypertension. Conn's disease (primary aldosteronism due to adrenocortical adenoma), is treated by surgical removal of the adenoma or unilateral adrenalectomy. This usually relieves all symptoms, including hypertension, dramatically. In primary aldosteronism due to adrenocortical hyperplasia, suppression therapy with dexamethasone should be first attempted, since this will cause complete remission of symptoms in patients with the "glucocorticoid-remediable" type of hyperplasia. If this fails, surgical intervention, consisting of partial, unilateral, or bilateral adrenalectomy, is required. The treatment of aldosteronism resulting from carcinoma of the adrenal cortex is surgical removal of the tumor. When extra-adrenal metastatic lesions are present, treatment with o,p'DDD, aminogluthetimide, or fluorouracil may temporarily alleviate the symptoms; however, no permanent remission is to be expected.

Licorice-Induced Pseudoaldosteronism

A syndrome consisting of hypertension, hypokalemia, suppressed plasma renin activity, and *low* aldosterone secretion after prolonged and excessive ingestion of licorice has been described by Conn et al.¹³ That licorice, the active principle of which is glycyrrhizic acid (a glycoside consisting of two molecules of glucuronic acid and one of a triterpene, glycyrrhetic acid), can induce salt retention, edema, and hypertension, has been known for some time.¹⁴⁻⁷⁷ This syndrome mimics primary aldosteronism. The mechanism involved is most probably related to the sodium-retaining properties of licorice. Possibly similar syndromes may result from excessive ingestion of other salt-retaining foods. Discontinuation of the ingestion of licorice resulted in the disappearance of all symptoms, including hypertension.

Hypercorticotesteronism

Corticosterone is an adrenal steroid with both glucocorticoid and mineralocorticoid activity. It is the major corticosteroid secreted in rodents. In man, the secretion rate of corticosterone is about five times lower than that of cortisol, and 20 times higher than that of aldosterone. Also, corticosterone, if compared with cortisol on a per milligram basis, is a much less potent glucocorticoid. This explains why hypersecretion of corticosterone results in a clinical picture resembling hyperaldosteronism but not hypercortisolism.

Hypercorticotesteronism may result either from a hyperplastic adrenal gland with a 17α -hydroxylase deficiency (a syndrome discussed below under congenital adrenal hyperplasia), or from a corticosterone-secreting adrenocortical tumor. Only two cases of such tumors have been described.^{26, 93} The clinical picture is that of aldosteronism. Suppressed plasma renin activity (stemming from corticosterone-induced sodium retention and hypervolemia), hypokalemic alkalosis, and hypertension are present. Aldosterone secretion is within the normal range (lack of suppression of aldosterone in a patient with corticosterone-secreting tumor indicates that aldosterone was secreted by the tumor). Treatment consists of surgical removal of the tumor; when metastases are present, administration of o,p'DDD, aminoglutethimide, or other "tumor-stabilizing" agents may result in temporary remission.

DISORDERS RESULTING FROM A DEFECTIVE HYDROXYLATION SYSTEM OF THE ADRENALS (CONGENITAL ADRENAL HYPERPLASIA)

Several defects in the hydroxylation system of the adrenal cortex have been described.^{5, 8} The enzymes which may be affected are: 21 -hydroxylase, 11β -hydroxylase, 3β -hydroxysteroid dehydrogenase, 17α -hydroxylase, and 18 -hydroxylase (Fig. 2). Patients with deficiency of any of the first three enzymes exhibit signs of hyperandrogenism (increased production of adrenal androgens is a result of the following sequence of events: decreased synthesis of cortisol $\rightarrow$ decreased negative feedback to the pituitary $\rightarrow$ increased ACTH secretion $\rightarrow$ adrenocortical hyperplasia $\rightarrow$ increased production of steroid precursors prior to the enzymatic block, mainly 17α -hydroxypregnenolone, which are largely converted to androgenic steroids). Patients with 11β -hydroxylase and 17α -hydroxylase deficiency invariably have hypertension.

11 β -Hydroxylase Deficiency

In this variant of congenital adrenal hyperplasia, there is an increased production of 11 -desoxycortisol (S_R) and 11 -desoxycorticosterone (DOC). DOC is a potent mineralocorticoid (although on a per milligram basis, it is 30 times less potent than aldosterone) and causes sodium retention and hypertension. Plasma renin activity is suppressed (due to sodium retention and hypervolemia), there is hypokalemic alkalosis, hypertension, and decreased aldosterone levels. Suppression with dexamethasone

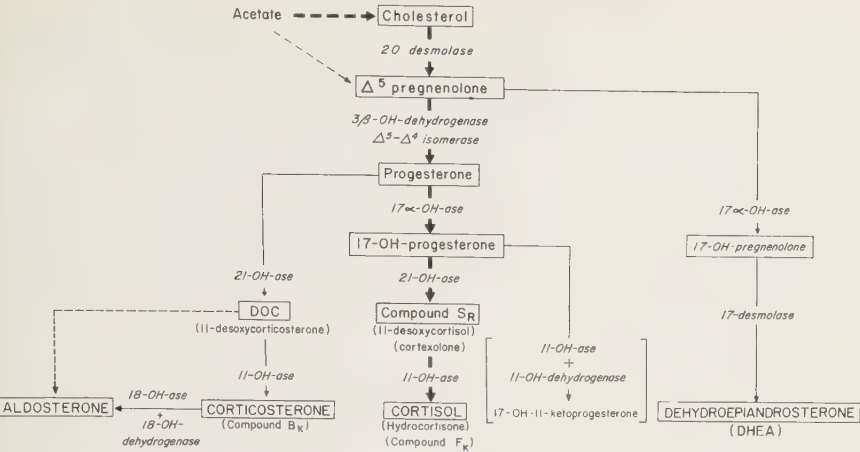


Figure 2. Major biosynthetic pathways of adrenocortical steroids.

methasone results in a drastic reduction in the secretion rate of DOC, and, if maintained long enough, in the reversal of all findings, including hypertension. These patients exhibit signs of hyperandrogenism (hirsutism and virilization in females, precocious puberty in children) due to an increased production of adrenal androgens. An increased production of ACTH, due to deficient feed-back by cortisol, leads to adrenal hyperplasia.

Secretion of DOC may be also occasionally increased in disorders other than congenital adrenal hyperplasia: Cushing's syndrome due to hyperplasia, ectopic ACTH syndrome, and adrenal malignancy.⁷⁸ This points to a partial 11 β -hydroxylase deficiency in these cases.

17 α -Hydroxylase Deficiency

This disorder, caused by an increased production of 11-desoxycorticosterone and corticosterone (both are mineralocorticoids), is also characterized by hypokalemic alkalosis, suppressed plasma renin activity, low aldosterone secretion, and hypertension. Thus, except for the low aldosterone level, this syndrome closely resembles primary aldosteronism, particularly since no hyperandrogenism is present; the deficiency of 17 α -hydroxylase results in insufficient production of immediate precursors of adrenal androgens. Moreover, since the 17 α -hydroxylase deficiency encompasses also the two other steroid producing glands, ovaries and testes, it leads to a decreased production of gonadal hormones by these organs, and signs of primary hypogonadism.

In some cases of hypertensive congenital adrenal hyperplasia, aldosterone secretion may be increased^{56, 63} in spite of sodium retention, hypervolemia, and suppressed renin activity resulting from excessive production of DOC or corticosterone. This is however very rare, and aldosteronism (instead of aldosteronopenia) may be accounted for by greatly enhanced production of aldosterone precursors, which leads to

excessive aldosterone production despite the suppressed renin-angiotensin feedback mechanism.

Treatment of both 11β -hydroxylase deficiency and 17α -hydroxylase deficiency consists of administration of cortisol or its synthetic analogues, which suppress pituitary ACTH production. This results in a complete reversal of all abnormal findings, including hypertension. Steroid administration must be continued for the patient's lifetime.

We close with a trite but important admonition. "Endocrine hypertension" is uncommon, but this is of no consolation to the patient who suffers from it. The physician must remain sensitized to its existence; he may be able to provide a cure.

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Hypertension and Renal Disease in Pregnancy

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There are many excellent texts on the subject of hypertension and renal disease in pregnancy. It is not my intention to recount standard teachings in this field, but to deal with controversial aspects. Recent changes in attitude to this group of diseases will be emphasized and, in particular, correlation of the literature on the difficult questions of weight gain, and sodium and water retention in pregnancy will be attempted. Some changes in the treatment of the pregnant and toxemic patient will be suggested. The subjects dealt with are: definitions and classification; renal biopsy and renal pathology; water, salt, weight and edema; uric acid and preeclampsia; prophylaxis and therapy of preeclampsia; non-toxemic hypertension; renal disease and pregnancy.

DEFINITIONS AND CLASSIFICATION

Our renal biopsy studies in pregnant patients with hypertension or proteinuria or both have led us to vary somewhat the current classification of toxemia of the American Committee of Maternal Welfare.^{72, 79} We have used the term "toxemia" to describe the *clinical* syndrome of hypertension or proteinuria; either sign may occur alone or with edema. Edema alone is not usually considered pathological (this statement will be discussed further). This syndrome can be caused by preeclampsia-eclampsia, by chronic hypertensive vascular disease, or a variety of renal diseases (either primary, or disease with renal involvement). Any of these diseases may occur singly or in combination during pregnancy.

Preeclampsia-eclampsia and renal diseases can be diagnosed with certainty by renal biopsy in the great majority of cases, and chronic hypertensive disease can often be recognized, although, in its earlier phases, the kidneys may be histologically normal. No systematic attempt

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in pregnancy to delineate the several causes of chronic hypertension, such as renal artery stenosis or pheochromocytoma, has yet been reported. Most cases of hypertension antedating pregnancy, or starting early in pregnancy, have been accepted as instances of essential hypertension.

We have questioned the limitation of the diagnosis of preeclampsia to after the twenty-fourth week of pregnancy only, as we have found five instances of the onset of preeclampsia earlier than the twenty-fourth week, confirmed by renal biopsy.⁷⁹

The toxemic syndrome may also occur early in pregnancy in association with hydrops fetalis due to Rh iso-immunization, but in this situation gross edema seems predominant. Proteinuria sometimes occurs, and hypertension is uncommon and usually mild.^{7, 19, 31, 66} I have seen two instances of this syndrome. In the first patient, the condition manifested as a nephrotic syndrome which regressed soon after delivery; the second patient had gross edema, oliguria, mild proteinuria, slight hypertension, anemia, and unexplained tachycardia. Her hydropic, still-born fetus weighed 1 pound 14 ounces, and the soft, friable placenta weighed 3 pounds 6 ounces. She, too, recovered slowly after delivery. Renal biopsy studies have not yet been reported in this interesting syndrome. There is a long-recognized association between hydatidiform mole and the toxemia syndrome.

A further interesting question has arisen with respect to the association of toxemia of pregnancy and abruptio placentae. López-Llera and Rubio⁵² performed renal biopsy after delivery in 8 patients who had severe abruptio placentae. Only 1 of the 8 patients had signs of clinical toxemia at the time of hemorrhage, although no data is given regarding the clinical course prior to detachment. Twelve-month follow-up revealed that only 1 patient had "questionable" prehypertension. Six of the renal biopsies showed a grade I pre-eclamptic glomerular lesion; two were normal. In view of the findings by Hibbard,³⁸ in his review of 23,043 deliveries, that neither preeclampsia nor essential hypertension is a significant etiological factor in abruptio placentae, and in view of the very low incidence of toxemia in the series of Kimbrough⁴⁴ and Hendelman and Fraser,³⁷ it seems quite likely that abruptio placentae may be another *cause* of the toxemia syndrome, and that the frequent proteinuria and hypertension accompanying an episode of abruptio placentae may result from the severe anatomical and physiological derangement of the acute episode. This conclusion must await further clarification.

RENAL BIOPSY AND RENAL PATHOLOGY

Many workers have reported on series of renal biopsies in pregnancy since Dieckmann's²⁶ first report in 1954. In 1965, we reported our experience with bleeding following needle biopsy in pregnancy.⁷⁷ Ninety biopsies were performed and showed a 16.7 per cent incidence of gross hematuria when done in late pregnancy on hypertensive patients. There was one death; surgical intervention was necessary twice, and four peri-

renal hematomas occurred. We recommended that, when renal biopsy was deemed necessary for diagnosis in the toxemia syndrome, it could often be deferred until a few days after delivery, when it is technically much easier and safer. At present, a clinical diagnosis of the cause of the toxemia syndrome can be made with sufficient accuracy to permit therapy in acute situations in late pregnancy. At other times, particularly before the third trimester, complete therapy may depend on pathologic diagnosis.

At present there is general agreement as to the renal lesions of preeclampsia, with minor disagreement as to the specificity of the glomerular lesions. Forty biopsies made subsequent to the first series reported in our laboratory have confirmed the original findings.^{70, 72} In addition, we found several instances of moderately severe nephrosclerosis in Negro patients under 20 years of age who had no previous history of hypertension. There were also two instances of arteriolar nephrosclerosis appearing *de novo* in subsequent biopsies after preeclampsia, and two further instances of progress in underlying arteriolar sclerosis which was evident in serial biopsies taken 11 days to 9 months after pregnancies with preeclampsia.⁷⁹

The renal pathology of preeclampsia may be summarized as follows:

GLOMERULI. There is diffuse enlargement of glomeruli, owing primarily to swelling of both endothelial and epithelial cells of the glomerular capillaries. We surmise that this swelling must be due to an increase of intracellular water as the solvent, because no increase in fat has been found. The glomeruli appear relatively bloodless. Mesangial or axial cells show minor degrees of proliferation and swelling. Deposits of basement membrane-like material are sometimes present beneath the endothelial cells and between the mesangial cells. These deposits have been shown to be probably fibrinogen, using a fluorescein-labeled antifibrinogen serum.⁶⁰ These deposits appear, to us, to be most prominent and profuse in the clinically severe illnesses which go on for 2 weeks or longer.

JUXTAGLOMERULAR APPARATUS. Pollak and Nettles⁷² recorded their impression that the juxtaglomerular apparatus was seen more often and was enlarged in patients with preeclampsia. Study of further patients confirmed this impression, and I made an attempt to count the cells and granules of the juxtaglomerular apparatus in preeclampsia. This failed because of the relatively scanty material in renal biopsies. Altchek et al.¹ have confirmed this finding of juxtaglomerular apparatus hypertrophy and also noted that swelling, degranulation, and vacuolation of the cells were prominent. Paradoxically, the macula densa cells were generally small, atrophic, and inactive.

Renin is produced by the juxtaglomerular apparatus, and it is interesting to speculate on the relationship between these findings and the demonstration of low serum renin levels in preeclampsia.¹¹

TUBULES. Changes in the tubules are nonspecific and consist mainly of granularity, vacuolation, and fatty change in cells. Some dilatation of the lumens occurs, and atrophy and basement membrane thickening is unusual. Proteinaceous material is often seen in the lumens. Altchek

et al.¹ noted severe degeneration of the cells of Henle's loop, with pyknosis and fragmentation of nuclei. The cytoplasm was often swollen and vacuolated, and occasionally pigmented. Severe lesions also involved the ascending limb of Henle and the beginning of the distal convoluted tubule.

INTERSTITIAL TISSUE. Edema is frequent, and fibrosis and chronic inflammatory cells are occasionally seen.

BLOOD VESSELS. Swelling of arteriolar walls, apparently due mostly to edema, but partly to hypertrophy, is frequent. This swelling sometimes encroaches upon and narrows the vessel lumen.

REVERSIBILITY. The majority of the lesions described are reversible, with the occasional exception of patchy glomerular basement membrane thickening and development or aggravation of fibrosis in arterial and arteriolar walls.^{78, 79} It has been our impression that patients who show these permanent changes are predominantly those who have developed severe early preeclampsia which has been allowed to go on for 2 or more weeks, and that underlying chronic hypertensive disease is more common in these patients than in those who do not manifest permanent changes.

WATER, SALT, WEIGHT, AND EDEMA

Obstetricians have invested weight gain, obesity, and edema with great diagnostic and prognostic significance since the classical reports of Zangemeister⁹⁹ and Cummings.²⁰ Preoccupation with edema has been justified by the inference that since it is present in such diverse diseases as cirrhosis, the nephrotic syndrome, heart disease, and nutritional deficiency, its presence in pregnancy must be a sign of disorder. In addition, some preeclamptic patients become very edematous, and reduction in edema sometimes occurs when other signs of the disease regress. Thus edema, in otherwise normal pregnancies, has been treated, often strenuously, by sodium chloride restriction and a variety of powerful diuretics; rapid weight gain, and even established obesity, have been vigorously treated by diet and diuresis.

Until recently there has been general acceptance of the view that preeclamptic patients retain excessive water, and that the "cause" of this is either excessive intake of sodium or inability of the kidneys to excrete sodium.

Recent reports, however, call into grave doubt many of these dogmas, and there is real question of the efficacy, and sometimes the safety, of the classical treatment of edema and obesity by sodium chloride restriction, diuretics, and strenuous dieting.

Weight Gain, Edema, and Water Retention

Even excluding the weight of the fetus and secundine, the majority of women gain weight steadily during pregnancy, although, as pointed out by Hytten and Leitch,⁴⁰ there is very little useful information in the literature about the optimum, or even average, weight gain, owing to many modifying factors in reported series. These authors made a de-

tailed analysis of the numerous sources of error in assessing the components of this weight gain and concluded that water and fat account for the greater part of the gain. No more protein is laid down than is accounted for in the fetus and in maternal organs such as the uterus and breasts and in the expanded blood volume. They also indicated the great difficulties inherent in using tracer elements for measuring body water. These difficulties apply equally to measurements of water retention in toxemia of pregnancy.

A majority of published figures^{17, 34, 65} show that the average weight gain in pregnancy is greater for patients with toxemia than for normal patients, but *prediction* of toxemia of late pregnancy by serial measurement of weight gain does not survive statistical analysis.

Fish et al.²⁹ analyzed the relationship between weight gain and toxemia in 1000 women in a private practice. Only 16 of these women developed toxemia. Of this group, 44.8 per cent gained more than 25 pounds, and 31.5 per cent gained more than 30 pounds, or more than 8 pounds per month. More than half gained more than 6 pounds per month. In the same practice, another 50 patients who developed toxemia of pregnancy were also analyzed. Only 58 per cent of these gained more than 25 pounds. Using total weight gain or rate of weight gain as a criterion for the combined groups, these workers found that the incidence of toxemia was greater among the normal gainers than among the abnormal (high) gainers.

Chesley,¹⁷ analyzing 10,591 cases from the literature, found that 72 per cent of women with toxemia gained less than 30 pounds, while 88 per cent who gained more than 30 pounds did not have toxemia. He said, "If one were able to plot frequency distribution curves for total weight gains . . . it would seem that most of the toxemic patients would fall within the normal range, and nearly half would have less than average 'normal' gains."

Rhodes⁷³ analyzed weight gain in 29 eclamptic patients and 113 patients with varying degrees of preeclampsia. He found that eclamptics gain less weight than either healthy or preeclamptic patients. The mild preeclamptics gained more than the severe preeclamptics (means: 29 and 24 pounds). He also found that the lighter a patient is for her height (ponderal index) the more likely she is to develop eclampsia; the heavyweights are more prone to mild preeclampsia. Davey et al.²¹ found that patients who were hypertensive before 24 weeks of pregnancy, or who later became hypertensive, were significantly heavier throughout pregnancy than normal women, but there was no difference between the rate of gain of women who became hypertensive in pregnancy and normal women. Between 36 and 38 weeks only, preeclamptic women gained weight at a significantly greater rate than before.

Pedlow⁶⁹ studied weight gains between the twentieth and thirtieth, and between the thirtieth and thirty-sixth weeks of pregnancy in 500 patients, and found that rate of weight gain during these two periods did not permit selection of patients who were destined to develop preeclampsia.

It seems quite clear from these figures, that any reliance upon rapid

weight gain in pregnancy as an indicator of developing preeclampsia is entirely misplaced.

Edema

Edema is commonly present in normal pregnancy. Thomson et al.⁸⁷ reviewed 24,079 pregnancies and reported that edema occurred in 35 per cent of normal pregnancies. It occurred in 60 per cent of women with hypertension and in 85 per cent with hypertension and proteinuria. Only when the diastolic blood pressure was above 90 mm. Hg was there a higher incidence of edema. All women with edema had a higher rate of weight gain than non-edematous women. Babies born to edematous women (both normal and preeclamptic) were heavier than those born to non-edematous mothers. These authors concluded that edema in pregnancy may be physiological and not, in itself, an ominous sign.

The pathogenesis of edema in pregnancy is not yet clear, and it is likely that more than one cause is involved and more than one type of edema occurs. Renin, aldosterone, and other steroids, including estrogen, antidiuretic hormone, and sodium retaining factor, as well as hypoproteinemia, excessive salt intake, mechanical pressure on lower limb venous systems, and even vascular damage, have all been implicated.^{32, 96} Edema fluid in pregnancy has been shown to contain amounts of sodium, potassium, and chloride equivalent to that in serum. Protein is present in small amounts.⁹⁶

Water

While edema is a sign of doubtful significance, the extent of retention of water in preeclampsia is also still poorly defined. Chesley,¹⁷ Hytten et al.,⁴¹ Hytten and Thomson,⁴² and MacGillivray,⁵⁴ have shown that large quantities of fluid are often retained by women who remain normotensive and who have normal infants, whereas many women who develop preeclampsia have total body water levels that are within normal limits. In fact, the severest forms of preeclampsia occur in those women who gain the least amounts of water and weight. Plentl and Gray⁷¹ found total body water to be the same in preeclamptics and normal subjects. Chesley¹⁷ pointed out that only 33 per cent of patients who gain water excessively in the last 10 weeks of pregnancy develop preeclampsia.

It is difficult to reconcile data on weight gain and water retention. There are still no conclusive data on the amount of fat and lean tissue retained in normal and abnormal pregnancy, but there are suggestions that fat is a major component of preeclamptic weight gain.^{73, 82} Yet, in a carefully controlled study, Thomson⁸⁸ was unable to show any significant reduction in albuminuria or perinatal mortality by preventing excess weight by dieting. Strict dieting should be advised with caution in the light of these statements and the findings by Singer et al.⁸¹ that high weight gain during pregnancy is related to higher infant birth weight, decreased prematurity rate, and also better growth and performance in the infant's first year of life.

Sodium in Pregnancy

The products of conception, the expanded blood volume, and the enlarged uterus and breasts of the pregnant woman require the reten-

tion of sodium during pregnancy. This demands new homeostatic settings in pregnancy and continuous variability of these settings. Edema in pregnancy is accompanied by further salt retention, and gross edema occurs in some patients with toxemia of pregnancy. Many workers have attempted to measure normal and abnormal sodium retention in pregnancy and to elucidate the mechanisms of retention, but confusion still reigns in this complex field.

Several approaches to this problem have been used:

1. Measurements of the sodium content of the body using radioactive ^{22}Na or ^{24}Na .
2. Measurements of urinary excretion rates of sodium under experimental conditions.
3. Metabolic balance studies.
4. Measurements of hormones known to have sodium-retaining or sodium-excreting actions.
5. Animal experiments.
6. Empirical treatment regimens.

1. **SODIUM CONTENT OF THE BODY.** Using radioactive ^{22}Na or ^{24}Na , Plentl and Gray,⁷¹ Dieckmann and Pottinger,²⁴ MacGillivray and Buchanan,⁵³ and Davey et al.²¹ have attempted measurement of total exchangeable sodium in normal and preeclamptic women. The first two groups found increased sodium and the last two groups found decreased sodium in preeclamptic women. As pointed out by Chesley,¹⁵ all these studies are open to criticisms which may partly invalidate their results.

MacGillivray and Buchanan⁵³ and Davey et al.²¹ used only urine radioactivity measurements, which are less accurate than the serum measurements used by the first two groups. Davey et al.²¹ used only an 18 hour equilibration period; the others (except Dieckmann and Pottinger) used a 24 hour period, and only 10 microcuries of ^{24}Na , which is less than other workers used. Even 24 hours is insufficient for full equilibration. Results differ, depending on whether the sodium space is expressed as an absolute figure, as a percentage of total body weight, as a percentage of total body water, or when it is corrected for height-weight or surface area. Each group has used somewhat different criteria. In all measurements involving total body weight, no means of measuring body fat content is available, and this factor would obviously influence results. None of these workers was able to account for the sodium which passed into the uterine contents or to find how long it took to get there.

Only Davey et al.²¹ made serial measurements, and their results showed great variation at different times in pregnancy. This variation has also been shown by Gray et al.³³ in serial studies of normal pregnant women. The work of Plentl and Gray⁷¹ seems open to the fewest criticisms, and, if we accept their data, it seems likely that preeclamptic patients retain sodium in excess of normal. Note, however, that these workers found *no* increase in body water in preeclampsics!

2. **SODIUM EXCRETION RATES.** Sodium excretion rates have been found to be consistently reduced in some pre-eclamptic and some chronically hypertensive women after the administration of a sodium load.^{16, 23, 97} This has always been taken to be evidence of inability of the kidneys of the preeclamptic patient to excrete sodium normally. The possibility that this finding could be an expression of sodium depletion

was never considered, but recent work by Sarles et al.⁷⁵ shows that this is indeed the case. Sarles et al. showed, in an excellent study, which included diagnosis by renal biopsy, that after a 10 to 12 day control period on an intake of 120 mEq. of sodium, the excretion rates of a 25 gm. sodium load were similar in normal, preeclamptic, and glomerulonephritic patients. Chronic hypertensives demonstrated a markedly *enhanced* excretion rate. This last finding was also described by Willson et al.⁹⁷ de Alvarez et al.²² were unable to demonstrate any difference in renal tubular reabsorption of sodium or water in normal and preeclamptic patients. These findings indicate strongly that preeclamptic patients on low sodium intake are sodium-depleted, and that when given sodium, they retain it avidly. They also demonstrate that, at least with respect to sodium handling, preeclampsics are distinguishable from chronic hypertensives.

After delivery edematous preeclamptic women excrete a greater amount of sodium in the first week than do normal women.¹⁵

3. BALANCE STUDIES. There are no entirely satisfactory metabolic balance studies in toxemia of pregnancy, which is not surprising when the difficulties, cost, and time required for such studies are considered. More restricted investigations, however, have produced useful data.

Gray et al.³³ varied the sodium intake of 28 institutionalized normal pregnant women during one month of their pregnancies. They showed a steady increase in total exchangeable sodium and total body water as pregnancy progressed. Those patients ingesting the largest quantities of sodium gained the most weight and had the largest amounts of total body water, but they retained significantly *smaller* amounts of sodium and had considerably lower secretion rates of aldosterone than those on the lowest intakes of sodium. These workers concluded that the usual home-prepared, low salt diet can be expected to have little if any effect upon the net retention of sodium in pregnancy.

In a study designed to test the ability of the kidney in pregnancy to retain sodium in a situation of reduced intake, we have found, in two women in the middle trimester, that after achieving sodium balance on an intake of 6 to 8 gm. of sodium chloride per 24 hours, a period of 5 days was required to resume balance when sodium chloride intake was suddenly reduced to approximately 1 gm. per 24 hours. This is much longer than the 24 to 36 hours required in normal non-pregnant subjects in a similar situation. One of my pregnant subjects developed symptoms of weakness, clinical edema, a slight rise in blood pressure, and a serum sodium of 129 mEq. per liter on the third day of sodium depletion. These abnormalities rapidly disappeared when sodium balance was resumed on the fifth day.

4. HORMONE MEASUREMENTS. Reports of the occurrence of pre-eclampsia in patients with diabetes insipidus and in others with adrenal cortical insufficiency^{3, 5, 63} tend to rule out antidiuretic hormone and adrenal cortical hormones as playing a part in the pathogenesis of pre-eclampsia, although they may do so in a negative sense. Yet, it is of interest to note that Patterson⁶⁸ has found that antidiuretic hormone is excreted in the urine of preeclamptic patients and not in that of normal pregnant women. We have shown that the infusion of physiologic

amounts of 8-arginine vasopressin in hydrated subjects caused substantial natriuresis in the middle trimester of pregnancy, and to a lesser extent in the third trimester.⁹⁰ This finding may explain why increasing the water intake in the hydration therapy of Turner and Fair⁹² results in a diminished sodium excretion in preeclamptic patients. Patients show subjective and objective improvement on this therapy.

Renin output is stimulated by reduced pulse pressure, often resulting from reduced plasma sodium concentration. It is significant that in normal pregnancy plasma renin levels are tremendously increased,⁹ indicating increased hormone action to retain sodium. This conclusion is supported by the finding of raised aldosterone secretion rates in pregnancy by Watanabe et al.⁹⁵ and Gray et al.,³³ and by their finding that secretion rates are inversely related to ingested sodium. In preeclampsia, both renin and aldosterone levels are lower than in normal pregnant women,^{11, 47, 93} and this finding is harder to explain; either the sodium already retained or some other factor cuts off this mechanism, or the mechanism is in a state of exhaustion following prolonged attempts to repair sodium deficiency. It is also possible that some of the hormone is produced by the placenta, and that this source of supply may be reduced. In this regard, it is notable that renin has been shown to be present in very large amounts in normal human amniotic fluid,¹⁰ and a renin-like substance in the placentas of normal and toxemic patients in equal amounts by Hodari et al.³⁹

Interesting data are also beginning to accumulate on the response of pregnant women to angiotensin, which in nonpregnant patients is both a vascular pressor agent and directly sodium-retaining. In nonpregnant patients with essential hypertension, it is paradoxically natriuretic.⁴ Normotensive pregnant women are relatively resistant to the pressor effects of angiotensin II and also show smaller reductions in sodium and chloride excretion than do nonpregnant subjects.¹⁸ Preeclamptic patients, on the other hand, show an increased pressor response to angiotensin.⁸⁵ Sodium excretion responses to angiotensin have not yet been measured in preeclamptic patients.

Hormone interrelationships in pregnancy and toxemia are very complex and are far from being well understood at present.

5. ANIMAL EXPERIMENTS. Unfortunately, no animal is known to suffer from a disease close enough to preeclampsia to provide a useful experimental model; yet, some guidelines may be obtained from pertinent experiments.

Kirksey et al.⁴⁵ and Wardlow and Pike⁹⁴ have studied the effects of varying sodium intake in pregnant rats. Rats fed a low-sodium diet showed general languor and debility, ate less food, and gained less weight than those receiving control or high sodium intakes. Dietary intakes 10 times greater than the control level were excreted by the kidneys, without disturbance. During sodium deprivation, many of the maternal tissues showed a marked intracellular decrease of sodium and an increase in potassium and water, but the fetal electrolyte levels were unaffected. Many of the changes found in maternal tissues of sodium-depleted rats are similar to changes found in human preeclampsia. Reducing the levels of sodium intake led to an increase in juxtaglomeru-

lar granulation and zona glomerulosa width. Very low sodium intakes led to degranulation of juxtaglomerular apparatuses. These experiments indicate that a low sodium intake provokes disorder in pregnant female rats, but that a high sodium intake is harmless.

Lichten⁵¹ has shown that normal pregnant rats show a net accumulation of approximately 83 mEq. of sodium per kg. of weight throughout gestation. Sixty-two per cent of the accumulation occurred in the third trimester. Analysis of postpartum sodium balance showed a continuing *retention* of sodium for 3 weeks. Analysis of the gravid uterus and its contents showed that all the retained sodium could be accounted for in these tissues. Near-term pregnant rats showed diminished ability to excrete water but no impairment in sodium excretion. If these findings are at all transposable to human physiology, they confirm the increased demand for sodium during pregnancy and imply that the mechanism for retention of sodium may be fully taxed by these requirements.

Treatment Regimens

It is in the use of sodium in prevention and treatment of preeclampsia and edema of pregnancy that the greatest confusion has arisen. Unsupported statements of opinion abound in the literature, and properly controlled experiments are infrequent. As mentioned earlier, the justification for sodium restriction in pregnancy is based partly on the frequency of edema in normal and abnormal pregnancies and the successful treatment of edema in other unrelated medical diseases. Perusal of the three papers written over 30 years ago most often quoted in support of this restriction^{35, 83, 84} show them to be quite unacceptable as scientific evidence, owing to the very small numbers of patients treated, doubtful criteria of diagnosis, great variability of response to administered sodium, unwarranted assumptions of fact, lack of controls, and intervention of many variables. A number of papers recommending sodium restriction in pregnancy have used this modality in combination with many other therapeutic measures, making impossible the assessment of the effect of sodium depletion alone. In addition, the measurement of sodium intake in many studies is far from accurate. Truly low sodium diets are difficult to achieve and are most unpalatable.

Dieckmann et al.²⁵ made a double-blind trial of high and low sodium intakes in pregnant patients who had rapid weight gain, edema, proteinuria, or hypertension, or a combination of these signs. The period of time on each regimen was not clearly specified but seemed to vary from 1 to 3 weeks, and separation of groups according to diagnosis was not made. Nevertheless the results are instructive. Sixty-three per cent of the patients showed no edema, or no change in the degree of edema, while receiving a supplement of 7 gm. of sodium chloride or 7 gm. of sodium bicarbonate. Sixty-six per cent showed no edema or no change after administration of 7 gm. of ammonium chloride or a placebo, lactose. Twelve per cent with edema showed a *decrease* of edema after administration of sodium salts. Only 25 per cent had an increase of edema. Regarding changes in blood pressure, only 9 per cent of the patients showed an increase of 20 mm. Hg or more systolic blood pressure while receiving sodium supplements. Ten per cent with a blood pressure of 140/90 mm. Hg or more showed decreases of 10 mm. or

more after ingestion of extra sodium. While receiving extra sodium, 75 per cent did not develop proteinuria and 17 per cent showed decreases in proteinuria, whereas only 8 per cent showed increases. Although Dieckmann did not analyze separately the 25 per cent of patients with preeclampsia, and there were no normal controls, the conclusion that extra sodium chloride is either beneficial or at least harmless to the great majority of pregnant patients with edema, rapid weight gain, proteinuria, or edema is inescapable.

In a recent double-blind study, Rodriguez and Schewitz followed 60 patients with varying degrees of chronic hypertension in pregnancy, from earlier than the twentieth week up to time of delivery, during which time the patients received a 9 gm. supplement of sodium chloride or a placebo each day until the end of pregnancy. Apart from learning that approximately 50 per cent of patients fail to take their medication or follow their diet, we found that only one patient developed superimposed preeclampsia, and she was receiving the placebo. Less edema occurred in the patients taking the salt supplement. Serum electrolyte and nitrogenous products and blood pressure data are being analyzed and will be published.

Three young patients in my private practice who had had malignant hypertension prior to pregnancy and were well controlled on hypotensive medication were followed through four pregnancies, during which they took diets high in protein and sodium chloride content (estimated at 8 to 14 gm. sodium chloride per day). In all three patients, the blood pressure was lower in pregnancy than before, and all patients had edema-free, uneventful pregnancies and delivered live infants.

Chesley and Annitto¹³ selected 237 pregnant patients who were found to be retaining excessive water for a trial of dietary sodium restriction. A control group received no dietary restriction; a second group was given a 1200 calorie, 2 gm. salt diet, and fluids were restricted to 1000 ml. per day; a third group was given the same diet but were told to force fluids. Unfortunately, these workers moved patients into the control group during the study period if they were found to be taking extra salt. They found the same incidence of preeclampsia in the controls as in the group under salt and water restriction, while the salt-restricted, forced-fluids group had one third the incidence of preeclampsia. They themselves pointed out that there were not enough cases to warrant statistically sound conclusions, and they carefully analyzed and showed only slight preponderance of some factors making for chance selection in any group. In passing, they noted that rapid weight gain bore no relation to the subsequent appearance of preeclampsia. These authors arrived at the surprising conclusion that "proved salt restriction seemed to reduce the incidence of preeclampsia in clinically normal patients who had occult edema." What their data does seem to me to show is that the control group was invalidated by adding to it patients who took partial treatment, and that the incidence of preeclampsia in this experiment was reduced by forcing fluids, and was unaffected by salt restriction.*

*Recently, Chesley has indicated (in a personal communication) that inclusion of multiparous patients in this study further reduced its validity. This criticism applies equally to the study by Robinson described in the next paragraph.

Robinson,⁷⁴ in an often quoted but not yet repeated experiment, found that a group of 1019 normal pregnant patients told to take extra salt in their diets had a significantly *lower* incidence of toxemia, edema, perinatal deaths, and bleeding during pregnancy than a group of 1000 matched patients told to reduce their dietary salt intake. Unfortunately, there were no measurements of salt intake or output in the patients, but the large numbers involved seem to provide statistical validity.

In the treatment of pregnant patients with established toxemia, there are three studies in which sodium chloride intake was varied. Bower⁶ studied two groups of patients admitted to hospitals in England and in Toronto, Canada, with toxemia of pregnancy. In the English series, three diets containing 2, 10, or 25 gm. of sodium chloride per day were used. In the Canadian series, two diets containing either 1.5 or 10 gm. of salt daily were used. Blood pressure changes, surgical induction and cesarean section rates, perinatal mortality, length of hospital stay, and infant weights were analyzed. There were no statistically significant differences in any of the groups compared, although the trends were all in favor of the high salt diets.

Mengert and Tacchi⁵⁸ varied the sodium intake of 48 patients admitted to hospital with preeclampsia. Alternate patients received either 10 to 11.5 gm. or 0.9 to 1.7 gm. of sodium chloride daily. No other details of treatment were given in the paper, and the urine excretion rate of sodium was not recorded, although concentrations were given. Blood pressure data were not provided. However, the authors stated that the two groups showed no significant differences by the criteria studied (blood pressure, weight changes, proteinuria, fetal mortality, and length of hospital stay).

Zuspan and Bell¹⁰⁰ studied 17 normal patients, 5 mildly preeclamptic patients and 3 moderately preeclamptic patients with salt intakes varying from 1 to 5.5 gm. per day for periods of 5 to 14 days. The higher sodium intake groups, in general, showed varying degrees of positive sodium balance and slower weight loss at rest. There was no clinical difference between the control patients and the "salt-loaded" mild preeclamptics. The moderately preeclamptic group were said to have a "worsening of clinical symptoms" on higher sodium intakes, requiring administration of hydrochlorothiazide. They gained weight over the first 4 days of study. This paper does not provide pertinent clinical or biochemical data, particularly with respect to the 3 patients who were said to worsen clinically; the numbers studied are very small and provide no basis for statistical evaluation, and only averages of all measurements are given; the salt loading was only up to 5.5 gm. of sodium chloride, which is less than other workers have used; and some study periods were only 5 days, which seem too short for valid assessment. The positive sodium balance and slower weight loss of the "salt-loaded" groups carries no implication of clinical detriment, and the "clinical worsening" of moderate preeclamptics does not seem to me to provide any basis for valid scientific opinion on the effect of high-sodium diets in preeclampsia.

In considering the dangers of excessive sodium chloride intake in pregnancy, reference is often made to the infusions of 1000 ml. of 2.5 per cent saline in 30 to 40 minutes done by Dieckmann et al.²³ and Will-

son et al.⁹⁷ as a diagnostic test for preeclampsia. Both groups described aggravation of clinical symptoms in a minority of pregnant patients so tested. Note that only a very small minority of patients manifested deterioration. The majority of patients were clinically unchanged, and a third group showed clinical *improvement*. When deterioration occurred, it rapidly improved in 24 to 48 hours after infusion in almost every patient. It should also be noted that the intravenous infusion of 25 gm. of sodium chloride in less than 1 hour cannot be regarded as a physiologically reasonable dosage.

A dangerous although fortunately not too common complication of low salt diets and diuresis in preeclamptic women has recently been described, and I have seen its occurrence in 2 patients. This complication is vasomotor collapse during or soon after labor due to hyponatremia. Tatum and Mulé⁸⁶ described 16 instances of collapse after delivery in toxemic patients, all of whom were successfully treated by infusions of hypertonic or isotonic saline. Low serum sodium and chloride concentrations were found in all 8 patients thus studied.

Palomaki and Lindheimer⁶⁷ recently reported an important case of a woman to whom a 17 mEq. sodium intake and trichlormethiazide were given for preeclampsia superimposed on pre-existing hypertension. This patient's urine output decreased and the serum uric acid, creatinine, and urea nitrogen steadily rose, until a diagnosis of salt depletion was made. Clear improvement of renal function and urine flow resulted from increasing sodium intake to 206 mEq. daily, and a live infant was delivered after spontaneous labor at 38 weeks of pregnancy.

Mulé et al.⁶² also described a rise in the blood urea and uric acid concentrations, with renal functional deterioration, in 7 patients with preeclampsia on low salt diets; 6 of these had underlying cardiovascular hypertensive disease. In each, concomitant drop in the serum sodium concentration occurred. Two of these patients were given intravenous infusions of sodium chloride with rapid reduction of urea and uric acid serum levels and improvement in renal function. Neither patient had increased hypertension when given salt.

These findings are not surprising in the light of knowledge that essential hypertensives are frequently salt losers, and the demonstration by Sarles et al.⁷⁵ that pregnant patients with chronic hypertension are, likewise, unable to retain sodium normally. In addition, we have shown a linear correlation between urinary excretion of sodium and uric acid in normal pregnant subjects.⁹⁰

There have been reports, mostly based on clinical trials which were not designed to provide adequate safeguards for statistical validity,^{27, 28} that the prophylactic use of thiazide diuretics in pregnancy reduced the incidence of preeclampsia and fetal mortality. Finnerty and Bepko's study²⁷ was of 3083 normal patients, and they found evidence of vasoconstriction in 15 per cent of untreated patients, whereas vasoconstriction was found in 5 per cent of patients receiving prophylactic thiazides. There were 64 stillbirths and neonatal deaths in the untreated group, and only 9 in the treated group. These authors themselves point out that the trial was not designed as a double-blind study and that they have not analyzed other possible causes of perinatal mortality. Short-term thiazide

treatment probably causes greater loss of weight than dietary measures alone when used for treatment of preeclampsia,⁵⁹ but in view of recent findings already quoted, weight loss of this type is not necessarily desirable.

Two well-designed, double-blind trials of thiazide diuretics as a prophylaxis against preeclampsia have recently appeared.^{30, 46} Kraus' study,⁴⁶ in particular, is noteworthy for its large number of subjects (1030) and its excellent design. Neither study shows any significant difference in the incidence of preeclampsia or hypertension between the treated and placebo groups. Kraus et al.⁴⁶ concluded: "The rationale for using thiazides on toxemic patients and those with excessive weight gain, despite the relative safety of the drug, must be seriously questioned." Apart from the implication of thiazides in uncommon instances of neonatal thrombocytopenia, jaundice, and hemolysis, Kraus et al.⁴⁶ confirm the known uricosemic action of the drug, and to me, this seems to be an additional strong contraindication to its indiscriminate use, as serum uric acid levels are a most useful biochemical index of preeclampsia in patients who have not received thiazides.

URIC ACID AND PREECLAMPSIA

Serum uric acid has been shown to be selectively raised in preeclampsia.^{48, 57} Pollak and Nettles⁷² showed that this relationship was true in a study in which renal biopsy was used for diagnosis. Studies in our laboratories subsequent to the reported series support this finding and also confirm Hayashi's³⁶ demonstration of a markedly reduced renal clearance of uric acid in preeclampsia. Serum uric acid levels are of immense usefulness in the diagnosis of preeclampsia superimposed on chronic hypertensive vascular disease, provided that the patient has not been receiving thiazide diuretics.

PROPHYLAXIS AND THERAPY OF PREECLAMPSIA

In the light of the foregoing review, and in view of our persisting ignorance of the etiology of preeclampsia, it would seem that a policy of therapeutic nihilism is still very much in order at the present time. Joseph De Lee's dictum, "Primum non nocere," bears repeating. In this spirit, I would hope to be advising the course of least harm in the following schema of treatment.

DIET. For normal pregnant patients and for patients with preeclampsia or hypertension, I advise a high protein, high vitamin and a high or at least unrestricted sodium chloride intake. High calcium, high iron, and high fluid intakes are also recommended. Fats and carbohydrates are advised in moderate or low amounts, depending on the need to limit calories. I believe it unwise ever to limit the pregnant woman's calorie intake to less than approximately 1400 per day. The preponderance of evidence now gives very little justification for limiting the salt intake of pregnant patients, except those with valvular heart disease.

In my private practice, and while chief of service at Presbyterian-St. Luke's Hospital, Chicago, I have advised this diet for 7 years and, although no statistically valid conclusions can be made, have had no cause to regret it.

EDEMA. Edema in pregnant patients with no hypertension or proteinuria should not be treated with diuretics. I have found that in approximately 70 per cent of otherwise normal patients, increasing sodium chloride intake will lead to obvious regression of the swelling, although in about half of these there will be a transient increase of swelling, rarely lasting longer than 7 days. The remaining 30 per cent of patients show no change, or some increase, in edema while they remain normally ambulant. One patient (over the last 7 years) on this regimen, manifested preeclampsia. In addition, few cases of edema will fail to respond to 24 or more hours of bed rest in a lateral recumbent position.

PREECLAMPSIA. With the exception of the dietary measures described, and restriction of the use of diuretic drugs, I find no cause to vary from the standard treatment of preeclampsia, believing bed rest to be the most effective therapeutic measure yet proposed. Increasingly heavy sedation is required for progressive disease; convulsions must be prevented. I have found magnesium sulfate to be a satisfactory sedative for short-term treatment in moderate and severe cases, with the addition of morphine sulfate when analgesia is required. Perinatal mortality is not reduced by delaying termination of pregnancy for longer than 24 to 36 hours in severe or progressing preeclampsia or in eclampsia.

HYPERTENSION. The fact that a dropping blood pressure is usually an excellent index of improvement in over-all status does not justify the conclusion that hypotensive drugs should be used to cause a reduction in blood pressure in the usual cases of preeclampsia. The hypertension may be serving a teleological purpose, and marked artificial reduction may reduce blood flow to vital organs and the uterus, and thereby embarrass the fetus. Hypotensive therapy seems justified only when pressures are higher than 180/120 mm. Hg, because of the increasing risk of cerebral vascular accident and left ventricular failure with higher pressures.

OLIGURIA-ANURIA. In patients with severe preeclampsia or eclampsia, when oliguria is present and increasing, the following measures are advised. The specific gravity of the urine is tested. Quantities may be insufficient for the hydrometer, and for this eventuality all obstetric units should have available a Total Solids Meter.* If the specific gravity is over 1.020 the patient is suffering from dehydration and requires fluids. If the specific gravity is approximately 1.010, impending renal failure is probable. Two drugs may avert this. The first is chlorpromazine or promazine. A test dose of 12.5 mg. is given slowly, intravenously. If a hypotensive response does not occur, the dose is repeated. Urine flow is monitored quarter-hourly. If there is an increase in flow, further doses may be given every 2 to 6 hours while measures to empty the uterus are adopted. If this fails, mannitol, 12.5 gm., is slowly injected intravenously.

*American Optical Company make a satisfactory unit which measures specific gravity accurately in 1 drop of urine.

If urine flow increases, the dose is repeated; further infusions of 25 gm. may be given every 4 to 6 hours. Beware of hyponatremia which can result from the profuse diuresis which sometimes ensues. Failure of both these drugs requires adoption of standard measures of therapy for renal failure.

The intravenous injection of ethacrynic acid (50 mg., repeated once) with mannitol or of furosemide (40 mg., repeated once) has also been suggested in impending anuria.^{1a} We have not had occasion to assess this therapy personally.

NON-TOXEMIC HYPERTENSION

There are many excellent chapters on chronic hypertensive vascular disease in pregnancy, the best of which, in my opinion, appears in Barnes' textbook, *Medical Disorders in Obstetric Practice*.² Townsend⁹¹ has provided an exhaustive review of the literature on hypertension and pregnancy. It is the intention here to emphasize some recent changes in attitude to this disorder.

Definition

There is extensive discussion in the literature about the upper limit of normal blood pressure in pregnancy, all workers acknowledging the considerable variation possible in measurements of blood pressure by sphygmomanometer. Although data on blood pressure in early pregnancy are not extensive, my experience has been that there is a misdirected reliance on "basal" blood pressure readings. In our clinics it has been noted that the great majority of primigravidae gave a first blood pressure reading well below 120/80 mm. Hg, in spite of the usual outward manifestations of anxiety attendant upon a first visit to the prenatal clinic. A minority of patients have a first reading higher than 120/80 mm. Hg which often decreases after rest or sedation, or at subsequent visits. I believe that the tense situation of a first visit constitutes a pressor test, and the clinician should take cognizance of a first reading above 120/80 mm. Hg. The significance of this strict criterion is that there was an incidence of approximately 30 per cent of raised blood pressure levels in the last few weeks of pregnancy in a group in which the first blood pressure lay between 120/80 and 140/90 mm. Hg.⁸

A simple but potent factor causing false blood pressure readings has escaped comment in the literature. The well-known hypotensive effect of pressure by the gravid uterus on the inferior vena cava in the supine position may result in a 10 to 15 per cent incidence of shock-like symptoms, but it is less well known that almost 90 per cent of pregnant patients over the thirty-sixth week of pregnancy show a significant difference in blood pressure readings between the supine and sitting positions. Thus, the common practice of reading the blood pressure with the patient in the supine position results in a falsely low reading in a majority of patients. Blood pressure should always be taken during pregnancy with the patient in the sitting (or if this is not possible, the lateral supine) position.

Course of Pregnancy

Although maternal and perinatal mortalities are universally acknowledged to be high in chronic hypertensive patients, my experience has been in agreement with that of Barnes,² that the real risk to both mother and fetus lies in the development of superimposed preeclampsia. The great majority of patients with essential hypertension pass through pregnancy without mishap if preeclampsia does not develop, and, furthermore, the average birth weight of their infants is not significantly different from a normal group.^{49, 61} The foregoing statements do not apply when blood pressure readings are persistently higher than about 170/110 mm. Hg. The prognosis for both mother and infant is also worsened by increasing maternal age, cardiac enlargement, retinal changes, and proteinuria. In these situations there is risk of cardiac failure or cerebrovascular accident from the markedly raised blood pressure. In spite of this, it is surprising how patients with very high blood pressure occasionally pass through pregnancy uneventfully when they receive good prenatal care.

Collating a large number of series of hypertensive pregnant women leads to an expected incidence of preeclampsia of about 30 per cent. The diagnosis of superimposed preeclampsia is often very uncertain, particularly if rise in blood pressure is used as the main criterion. This is so because at least 20 per cent of hypertensives show a rise of blood pressure in the third trimester which is not a manifestation of preeclampsia.⁶¹ It is possible that this 30 per cent incidence of preeclampsia is too high. Barnes² found an incidence of preeclampsia of 11 per cent in a group of 100 pregnant women with essential hypertension, and Rodriguez and Schewitz (as previously mentioned) found only one instance of overt preeclampsia in a series of 60 essential hypertensives who were part of a double-blind trial of sodium chloride supplementation. We agree, also, that a mid-trimester drop in blood pressure carries implications of a good prognosis for both mother and fetus. This drop seems to occur in about 50 per cent of patients.¹⁴

Diagnosis of superimposed preeclampsia, which carries such important implications, should depend not only on blood pressure monitoring and development of edema and proteinuria, but also upon careful and frequent retinal evaluation and assessment of serum uric acid and urea nitrogen. In the absence of thiazide medication, a selective rise of the serum uric acid is a most valuable diagnostic feature of preeclampsia.

Treatment

The treatment measures already described for preeclampsia apply equally for patients with chronic hypertension in pregnancy. It is even more important, with these patients, to ensure an adequate intake of sodium chloride, in view of the well-documented tendency of patients with essential hypertension to be salt losers, even in pregnancy.⁷⁵ Our experience indicates that hypertensive patients who are urged to take an adequate quantity of salt, fluid, and protein feel well, develop less edema, and appear to have a low incidence of superimposed preeclampsia. Bed rest, as both a prophylactic and therapeutic measure, deserves emphasis.

The superimposition of preeclampsia upon chronic hypertension calls for hospitalization and careful observation. In the great majority of such instances—be the fetus small or large—no good purpose is served by delay in termination of the pregnancy. Fetal mortality is not reduced by delay; eclampsia and renal failure are an ever present risk, and the possibility of permanent renal damage seems to be present.^{78, 79}

Although this question is unresolved, hypotensive medication does not seem to have a large place in treatment at present. Landesman and Ollstein⁵⁰ found that reserpine failed to improve fetal outcome or incidence of superimposed toxemia when used for long periods in pregnancy. Hypotensive medication is probably of use only in acute hypertensive crises, where there is a risk of vascular rupture, cardiac failure, or renal failure. When such medication is used, too rapid or extensive reduction in blood pressure must be carefully avoided.

Patients who become pregnant while receiving already well-standardized hypotensive medication should continue to take these drugs; dosage adjustments can be made gradually, when necessary. I have had gratifying success with three young women who had previously had malignant hypertension, and whose blood pressures were well controlled on hypotensive drugs (methyl dopa, mecamylamine, and thiazides) when they became pregnant. All had uneventful pregnancies on high salt intakes, and minor reduction in dosages of their drugs was possible. One patient was able to discontinue all hypotensive medication in the last trimester of pregnancy.

RENAL DISEASE AND PREGNANCY

Apart from the kidney involvement of preeclampsia and essential hypertension, a great variety of other diseases of the urinary tract occur in pregnant women. Obstetricians have benefited by the explosion of knowledge which has followed the widespread use of renal biopsy, and there is a notable difference in the way the subject is treated in modern textbooks in comparison with those of just 20 years ago, when many renal diseases were grouped as “chronic nephritis” and treated as a single entity. Modern attitudes have been extensively reviewed in an excellent chapter by Nettles,⁶⁴ and the reader in search of detail is referred there.

Glomerulonephritis

Acute and chronic post-streptococcal glomerulonephritis occur in association with pregnancy, the chronic disease being seen in several forms and degrees of severity. Other forms of glomerulonephritis with a less well-defined pathogenesis and etiology also occur. The association is not common enough for dogmatic rules to be enunciated, but my experience over the past 17 years, added to recent reported series, permits some generalizations.^{55, 56, 76, 80, 89, 98}

Acute Nephritis

The association with pregnancy is uncommon and the treatment and prognosis are no different than in the non-pregnant state. The risk for the fetus is increased.

Chronic Nephritis

Many forms of chronic nephritis occur so rarely in association with pregnancy that no firm statements about them can be made. For instance, the effects of renal disease occurring with lupus erythematosus or diabetes depend partly on the severity of the generalized disease and partly on the renal functional effects.

The effects of chronic nephritis resulting from post-streptococcal nephritis depend on several factors. The most important, in our experience, has been the height of the blood pressure early in pregnancy. The higher this is, the poorer seems to be the prognosis for the fetus, and the greater the frequency of superimposed preeclampsia. As in essential hypertension, the greatest risk appears to be superimposed preeclampsia. Contrary to the findings of many other investigators, we have not found that mild or even moderate renal functional deterioration has worsened the prognosis in pregnancy to any great extent, provided that hypertension is not severe. We have had several patients with nitrogen retention of up to 100 mg. of serum urea nitrogen go through pregnancy without mishap. In this regard it is noteworthy that Bucht and Werkö¹² have shown that renal function is not compromised by pregnancy in patients with chronic glomerulonephritis in whom the blood pressure is not significantly elevated and renal function is not greatly decreased at the outset.

Proteinuria, of even severe degree, and edema seem to have minimal significance in guiding prognosis for a given pregnancy. Thus, the nephrotic syndrome has a surprisingly favorable outcome in the great majority of pregnancies. The risks in this syndrome are most particularly those of infection and thromboembolic phenomena. Preeclampsia is rare in association with the nephrotic syndrome.

In summary, it may be said that the presence of hypertension and severe functional deterioration in patients with chronic nephritis is of ill omen. Proteinuria, edema, and mild functional deterioration do not preclude reasonably safe and successful pregnancies.

Pyelonephritis

Infection of the lower urinary tract is very common in pregnancy, and if colony counts of bacteria are made, significant bacteriuria incidences of up to 6 per cent will be found.¹³ Because the risk of renal infection is high in these patients, active therapy with the appropriate antibiotic is indicated, with full anatomic evaluation in recurrent infections. Pyelitis and pyelonephritis also occur with some frequency and require vigorous therapy.

Chronic pyelonephritis is difficult both to define and to diagnose. However, established infections are frequently aggravated by preg-

nancy, are usually difficult to eradicate, and may, on occasion, be life-threatening. Recourse to nephrostomy drainage is sometimes necessary, and on rare occasions termination of pregnancy may be required. We regard renal infections during pregnancy with great concern.

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Diagnosis and Treatment of Lupus Nephritis

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Systemic lupus erythematosus (SLE) is a clinical syndrome of unknown cause, characterized by multi-system involvement and subject to multiple remissions and exacerbations. Since the discovery of the lupus erythematosus cell by Hargraves¹⁷ in 1948, SLE is no longer a medical rarity but a frequent occurrence in practices of physicians who are aware of the varied modes of expression of the disease process. There is some evidence that the actual incidence may also be rising. Systemic lupus erythematosus appears to be genetic and familial in nature. Family studies have shown a high incidence of abnormal immunological factors such as antinuclear factors in parents and siblings of patients with proven systemic lupus erythematosus.^{3, 30, 41} In certain susceptible individuals the disease process may be triggered (? induced *de novo*) by a variety of stimuli, such as sunlight, drugs, and chemicals.^{2, 28, 29} Although typically a disease of young women of childbearing age, SLE can affect individuals of all ages of either sex.

The introduction of corticosteroids into the management of SLE and its complications has resulted in a reduction of acute mortality, and the increased life-span of patients with SLE has allowed the full evolution of the disease process to become more fully known. SLE can affect virtually every organ system of the body, and renal involvement is very common. The incidence in published series has ranged from 50 to 80 per cent.^{10, 35, 38, 47, 49, 53, 54, 62, 63} Renal involvement has been shown to have great prognostic implications, and several studies have shown that the most common cause of death of patients with SLE is progressive renal impairment.^{10, 35}

In view of the frequency and seriousness of renal involvement, the recognition of lupus nephritis and the estimation of its severity is of greatest importance in the management of patients with SLE.

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PATHOGENESIS OF LUPUS NEPHRITIS

It might be helpful to discuss briefly what is known about the pathogenesis of lupus nephritis, so that we might better understand the therapeutic measures that have been proposed. The etiologic basis for SLE remains unknown but the pathogenesis of renal involvement has been shown to involve immunologic phenomena.

Two different and distinct pathogenetic mechanisms whereby host antibody production can cause glomerulonephritis have been demonstrated experimentally and appear to have their human counterpart.⁶ One of these mechanisms is dependent upon the host's ability to produce antibody directed against his own glomerular basement membrane. This mechanism is exemplified by nephrotoxic serum (Masugi) nephritis experimentally and by Goodpasture's disease in clinical cases.

The other pathogenetic mechanism of glomerulonephritis depends upon the production of antibodies which react with nonglomerular endogenous or exogenous antigens in the circulation. The resultant circulating antigen-antibody immune complexes are subsequently trapped in the glomerular capillary walls where further immunologic events, such as complement fixation, chemotaxis of polymorphonuclear leukocytes, and proteolysis, result in structural damage. This mechanism is typified in experimental animals by the serum sickness model of glomerulonephritis.

In man the antigen-antibody complex mechanism appears well established in the nephritis of systemic lupus erythematosus.²³ Patients with SLE form a spectrum of antibodies which react in various test systems with natural or autologous antigen. The most important and, perhaps, most specific of these antibody-antigen reacting systems is the DNA-anti-DNA system.

Several lines of investigation have supported this view of pathogenesis of lupus nephritis. Freedman and Markovitz¹² in 1962 were able to elute gamma globulin from glomeruli of patients with lupus nephritis, and demonstrated antibody-like activity of the gamma globulin against glomerular capillary wall antigens and other antigens. Several investigators have since demonstrated that antinuclear antibodies may be eluted from isolated glomeruli.^{25, 27, 35} These antibodies are directed against DNA, nucleoprotein, and other nuclear antigens. Koffler et al.²⁵ have shown that treatment of involved glomeruli with deoxyribonuclease, which is known to release antibody from DNA complexes, releases antibodies directed against DNA and nucleoprotein.

Utilizing fluorescein-labelled anti-DNA antibody, it is possible to detect DNA antigen in glomeruli in a distribution similar to that of gamma globulin.²⁵ Other immunologic reactants such as B₁C globulin have also been shown to deposit in the glomeruli, and the distribution and alterations in structural picture have been shown to closely resemble experimental serum sickness nephritis.^{24, 33, 39}

Studies of serial serum specimens from patients with SLE have also suggested the important role of the DNA-anti-DNA system. In contrast to other antinuclear antibodies, antibodies to DNA show specificity for

SLE.⁵⁷ Approximately 75 per cent of patients with active renal disease have either precipitating or complement-fixing antibodies to DNA, and the titer of anti-DNA antibodies fluctuates consistently with exacerbation and remission of the illness.^{40, 50}

The large amount of complement that deposits in the glomeruli is uniformly associated with depression in serum complement levels. Schur and Sandson⁵⁰ have reported the close correlation of low levels of serum complement, presence of complement-fixing antibodies to DNA, and active renal disease.

In the renal glomerulus, the pathogenic mechanism is expressed histologically in varied patterns. Patterns may range from hardly noticeable proliferation and focal changes to gross proliferation, wide-spread necrosis, basement membrane thickening, and glomerular obliteration. Using serial percutaneous renal biopsy, Muehrcke and his colleagues³⁸ described the spectrum of renal involvement in SLE.

PATHOLOGY OF LUPUS NEPHRITIS

Several other detailed investigations into the pathology of renal involvement in SLE have also been reported.^{4, 16, 43, 49, 53, 63} We shall summarize here some of the usual findings.

The renal changes observed on light microscopy were conveniently divided into four categories by Muehrcke, Pollak, and their colleagues.^{38, 43, 45} Changes in the kidney were assessed for severity of involvement and activity of lesions by a semiquantitative method which has been found useful in assessing follow-up biopsies:

1. *No renal involvement.* By light microscopy, the kidneys are quite normal in some patients with SLE. Muehrcke et al. studied 33 patients with SLE, with and without clinical evidence of renal involvement, and found that on renal biopsy, 10 had no involvement. Renal involvement by clinical or histologic assessment has been reported in from 50 to 80 per cent of patients with SLE; conversely, 20 to 50 per cent did not have renal involvement.

2. *Minimal glomerular involvement.* This category, also called lupus glomerulitis, is characterized histologically by mild focal and local changes in the glomerular tufts. The lesion consists of small areas of endothelial or axial hypercellularity, especially at the periphery of a glomerular tuft. In association with the cellular changes, there may be mild and irregular basement membrane thickening. There is no wide-spread disruption of tubular or interstitial tissue, and evidence of active lesions (necrosis, hematoxylin bodies, fibrinoid) is not present.

3. *Diffuse membranous glomerulonephropathy.* This lesion is characterized by diffuse thickening of the basement membrane of the capillary loop. There is usually no (or only a minor degree of) cellular proliferation and no evidence of active lesions.

4. *Lupus glomerulonephritis.* This lesion is characterized by more severe involvement of the glomeruli associated with interstitial and tubular abnormalities. Part of each glomerulus may be affected rather

than the whole glomerulus. Many glomeruli are severely involved in some cases; severe involvement may be focal in other cases. Local necrosis with obliteration of capillary loops, karyorrhexis, and fibrinoid changes are usually present. Hematoxylin bodies and hyaline thrombi are occasionally found. Proliferation of mesangial, epithelial, or endothelial cells is present in varying degrees, and epithelial crescents, while uncommon, may be seen. Moderate to severe focal tubular and interstitial changes, and, occasionally, foci of inflammatory cells resembling a granuloma are seen.

Electron microscopic studies of the renal injury in SLE have been reported.^{11, 16, 43} In the minimal or no involvement group, minor changes consisting of focal thickening of the basement membrane, focal fusion of foot processes, and focal osmiophilic deposits on either side of the basement membrane have been found. In the diffuse membranous lesion, electron microscopy has shown irregular "spikes" of the subepithelial aspect of the basement membrane, with osmiophilic material between the spikes. The picture is similar to idiopathic membranous glomerulopathy. In lupus glomerulonephritis the changes are usually quite marked, with focal fusion of foot processes and focal thickening of basement membrane. The most striking feature, however, is the presence of osmiophilic deposits, most commonly present on the endothelial side of the basement membrane, but also frequently present on the epithelial side and in the mesangial areas. In the more severely affected glomeruli, the deposits are granular and quite extensive. The deposits are felt to represent aggregations of immune complexes.

By immunofluorescence microscopy, IgG and B₁C globulin can be regularly detected in the glomerular capillary walls.^{24, 33} Less frequently, IgM and IgA have also been found, as well as fibrinogen.^{39, 55} The pattern of distribution of immunoglobulin and B₁C is highly variable. Koffler et al.²⁴ recently reported that the mesangial areas appear to be the initial site of IgG localization, followed by deposition along the basement membrane. In severely affected glomeruli, a coalescence of immunoglobulin occurs, giving rise to the lumpy, beaded pattern typical of immune complex-mediated glomerulonephritis. They suggested four patterns of immunofluorescent staining for IgG: mesangial, membranous, granular, and lumpy. The patterns appeared to be correlated to the presence of clinical renal disease. The linear membranous pattern and solitary mesangial depositions were present in kidneys of patients without clinical or other histologic evidence of glomerular injury.

The granular and lumpy patterns were associated with the presence of clinically apparent renal involvement. There was no correlation between the length of systemic illness and the pattern of immunofluorescent staining. IgG was the predominant immunoglobulin, being present in 15 of 19 cases. A recent report suggests that deposition of a specific subclass of IgG (IgG₂) may be associated with lupus nephritis.³¹

Kawano et al. have made an intriguing observation of virus-like structures in renal biopsies of patients with SLE.²¹ Whether these findings are indicative of a viral etiology of SLE or a secondary infection awaits further study.

MANIFESTATIONS OF RENAL INVOLVEMENT

The most common clinical abnormality in patients with lupus nephritis is significant proteinuria. In various studies, 50 to 90 per cent of patients with SLE have been found to have abnormal proteinuria. Soffer⁵⁴ found renal involvement in 56 of 90 patients studied by clinical tests. All with lupus nephritis had persistent significant proteinuria. Sixteen patients had the nephrotic syndrome. Pollak et al.⁴⁶ found that 12 of 23 patients with minimal involvement, 6 of 7 with membranous involvement, and 45 of 47 with lupus glomerulonephritis had greater than 200 mg. protein in a 24 hour urine collection. Nephrotic syndrome occurred in 1 of 7 patients with membranous change, and in 30 of 47 with lupus glomerulonephritis.

Abnormalities of urinary sediment are also frequent in lupus nephritis. An examination of a fresh early morning specimen should be part of every investigation of patients with SLE. Hematuria, usually microscopic, is invariably present in more severe cases. Large numbers of leukocytes in the urine without bacteriuria is associated most frequently with active glomerulonephritis. Casts are more frequent in patients with severe involvement. The telescoped urine sediment is found only in those with active lupus glomerulonephritis. In the study by Soffer, 88 per cent of patients with lupus nephritis had hematuria; 63 per cent had significant pyuria without infection, and 70 per cent had abnormal casts. Hematuria was found in 6 of 23 patients with minimal involvement and in 39 of 47 patients with active lupus glomerulonephritis by Pollak et al.⁴⁶ Renal function in lupus nephritis is generally well preserved except when the lesion shows active lupus glomerulonephritis. In this group half had elevated blood urea nitrogen and serum creatinine levels.

Elevated blood pressure is not usually present unless there is significant arteriolar and glomerular damage.

CLINICAL PATHOLOGICAL CORRELATION

If it were possible to accurately assess the amount of histologic damage by simple renal function tests and biochemical parameters, renal biopsy, with the attendant risks and morbidity, would not be necessary except in exceptional cases. Clinical-pathologic correlations have been made in a number of studies. Unfortunately the correlations are not strong enough to allow one to estimate histologic findings without biopsy.

In his study of 90 patients with SLE, 56 of whom had renal involvement, Soffer⁵⁴ was able to study the relationship of structural change and renal function in 19. Although, in general, those with no or minimal renal involvement had normal renal function and urinary sediments, there was no clear distinction among the groups that had more involved renal damage. In particular, blood urea nitrogen was a poor reflection of histologic damage unless the renal damage was severe.

In a more detailed study of 87 patients with SLE who were followed

from 7 months to 8 years, Pollak et al.⁴⁶ reported the failure of urinalysis and simple renal function tests to predict reliably the underlying renal pathology.

Of the 87 patients studied, 10 patients had normal findings, 23 had minimal involvement, 7 had diffuse membranous involvement, and 47 had active lupus glomerulonephritis on the initial renal biopsy. Fresh early morning urines were examined for cells, casts, and protein. Serum creatinine and serum urea nitrogen levels and creatinine and urea clearances were measured as parameters of renal function.

Significant numbers of erythrocytes and leukocytes were usually found in most patients with lupus glomerulonephritis, but were also occasionally found in patients with histologically normal kidneys, minimal involvement, and membranous change. In some patients with active lupus glomerulonephritis, no abnormality of urine sediment was found. Casts were generally found in patients with lupus glomerulonephritis but had no close correlation to underlying activity of disease process. The telescoped urine sediment was found only in active lupus glomerulonephritis. Although, in general, more severe renal damage was associated with abnormal sediments, there was no clear-cut differentiation among the four histologic groups, and, importantly, it was seen that active lupus glomerulonephritis could coexist with a normal-appearing sediment.

Significant proteinuria is frequently associated with renal involvement of every degree. No patient with normal kidneys had significant proteinuria, but 7 patients with minimal involvement and all but 9 with membranous or lupus glomerulonephritis had significant proteinuria. The magnitude of the proteinuria correlated well with the overall histologic severity, but not with the degree of histologic activity. The nephrotic syndrome was present in 1 of 7 patients with membranous glomerulopathy and in 30 of 47 with active lupus glomerulonephritis. The association of significant proteinuria with an abnormal sediment was invariably indicative of lupus glomerulonephritis.

Thus it can be seen that while general correlations are possible, there can be individual cases of lupus glomerulonephritis without significant proteinuria. Moreover in a patient with abnormal proteinuria an exacerbation of the disease may not be reflected in increased proteinuria.

With the tremendous amount of functional reserve that the kidneys have, it is not surprising that the serum creatinine and urea nitrogen levels were normal in all patients with normal kidneys, minimal involvement, and membranous glomerulopathy. In approximately half the patients with active lupus glomerulonephritis, the serum creatinine and urea nitrogen levels were elevated. In a detailed analysis, the creatinine and urea clearances correlated with overall histologic severity, but did not correlate with histologic activity.

Therefore, the elevation of creatinine and urea nitrogen indicated severe damage to the kidneys, but conversely, severe involvement could be present in the face of normal serum creatinine and urea nitrogen levels. Again activity or exacerbations of the disease process could not always be correlated to a fall in rate of creatinine or urea clearance.

Zweiman et al.⁶³ have confirmed the lack of correlation between presence or absence of clinical renal abnormalities and the degree of pathologic change. They found that 5 of 25 patients with lupus nephritis had no clinical abnormalities as measured by urine sediment, blood urea nitrogen or serum creatinine level and creatinine clearance. In contrast, 10 of 15 patients with no involvement or mild involvement on renal biopsy had definite abnormalities in the tests done. None of the 15 patients with normal or mild involvement had decreased renal function.

It appears that more sophisticated clinical tests may be necessary to accurately assess renal damage in SLE. Some have suspected that urinary gamma globulin excretion is increased in patients with lupus nephritis. Miyasoto et al.,³⁷ however, failed to confirm this finding.

SEROLOGIC FACTORS AND CLINICAL ACTIVITY

The serums of patients with active SLE often contain high titers of antibody to nuclear antigens and have low levels of complement. These immunologic abnormalities have been noted most frequently in patients with lupus nephritis. A number of studies have sought to determine the relation of clinical activity and renal involvement to these immunologic factors. If readily obtained immunologic parameters could reliably predict the underlying processes and activity, one could have a rational basis for therapy.

It was found that LE tests were more frequently positive during clinical activity and more frequently positive when fever was accompanied by evidence of more than one system involvement.⁴⁸ But the overlap was considerable, and several patients had positive LE tests with no relation to activity of disease. Excellent reviews of the LE test and antinuclear antibodies have recently appeared.^{8, 34}

Whole complement titer and, more specifically, the third component of complement (B_1C globulin) are often low in active SLE. A number of studies have shown good correlation between whole complement and titer of B_1C .^{19, 58} Townes⁵⁸ found that 60 of 80 patients with SLE had low total complement, whereas only small numbers of patients with scleroderma, discoid lupus, or rheumatoid arthritis with LE cells had low complement. Of 49 patients with active renal involvement, the complement titer was low in 47.

Gotoff et al.¹⁵ recently described 45 patients with SLE, 25 of whom had low B_1C levels. Of the 20 patients with active disease, 18 had low complement values. Values tended to return to normal with treatment. In patients with SLE, low levels of B_1C correlated directly with activity. However, not all patients with low levels of B_1C had renal disease. Similar results were reported by Humair.¹⁹

A detailed study of various immunologic factors and clinical activity in SLE was reported by Schur and Sandson.⁵⁰ Ninety-six patients were studied; 47 patients had renal disease. Certain immunologic factors were more common in patients with renal involvement than without: precipitating antibodies to DNA were found in 41 per cent, precipitating

antibodies to heat-denatured DNA in 59 per cent, free DNA in 7 per cent, and complement-fixing antibodies to DNA in 74 per cent. (The incidence for the group without renal disease was: precipitants to DNA in 5 per cent, to heat-denatured DNA in 24 per cent, free DNA in none, and complement-fixing antibodies to DNA in 48 per cent). Markedly depressed serum complement levels were found in 45 per cent of patients with renal disease as compared to only 5 per cent in patients without renal disease. Only 10 per cent of patients with active renal disease had normal complement. The combination of high titers of antibody to DNA and low complement values was found only in patients with active renal disease. Only one patient had an exacerbation of renal disease without a fall in complement level. Nineteen of 20 patients with exacerbation had greater than a 50 per cent fall in the preexisting level of complement. Other components of complement have also been studied in SLE. Kohler and Bensen²⁶ reported that C'1q, C'3, and C'4 were usually decreased, with a prolonged depression of C'4 being the most consistent finding.

Pincus et al.⁴⁰ have described a test to detect antibodies to DNA which is more sensitive than complement-fixing and precipitative methods. With their method, 75 per cent of SLE patients had abnormal DNA-binding serum activity. The level of DNA binding could be correlated to activity of disease, and of 45 patients with high levels of binding, 38 had active renal disease.

It is apparent from these studies that the immunologic process of injury in SLE is reflected in a variety of factors that are measurable in the serum. Unfortunately, several of the techniques are, as yet, tools of research and not clinically applicable, although one can foresee the day they may be widely available. Nevertheless, measurements of complement activity, B₂C globulin, and antinuclear antibodies are available in most laboratories of large hospitals or through special laboratories. Careful assessment of these factors is of great importance in the management of patients with SLE and particularly lupus nephritis.

NATURAL HISTORY OF RENAL LESION IN SLE

Renal involvement is frequent in SLE and serious in its implications. As cited previously, renal insufficiency has become the leading cause of death in SLE. This has led to the concept that renal involvement in SLE carries a bad prognosis for the patient and is invariably progressive. The picture has been painted too darkly, perhaps, because the variations in degree and severity of involvement have not been emphasized.

Long-term follow-up observations with serial renal biopsies have shown that long-term survival is clearly related to degree of histologic involvement and clinical impairment of renal function.^{38, 44, 45}

Patients with Normal Kidney on Initial Biopsy

Most patients without evidence of renal impairment early in the disease process have gone for many years with no evidence of renal involvement. Soffler felt that renal involvement, when it appeared,

appeared early and was particularly frequent in younger patients. However this is not invariably so, and we have seen patients develop renal involvement several years after the initial diagnosis.

Pollak et al.⁴⁵ found that of 10 patients with normal findings on initial biopsy, 9 were alive 2 to 8 years later. The only death was unrelated to renal disease. Only one patient developed subsequent renal involvement 23 months after the initial biopsy.

Minimal Glomerular Involvement

In earlier papers³⁸ it was felt that this lesion would progress to lupus glomerulonephritis and progressive renal insufficiency. However, large numbers of sequential renal biopsies have shown that the majority of patients with this lesion showed no progression of renal impairment, clinically or histologically.

Of 23 patients with mild renal involvement (lupus glomerulitis), 17 were alive at final follow-up, an average of 40 months. There was no evidence of progressive renal disease in any living patient. Two patients had died in renal failure. Serial biopsies were performed in only a small number of patients, since there was little clinical evidence of progression, and only 3 patients were felt to have developed lupus glomerulonephritis on biopsy. Two died; the other responded to large doses of steroids. Three additional patients died of causes unrelated to renal involvement.

Membranous Glomerulonephropathy

The number of patients with this lesion who have been studied with sequential biopsies has been small, but there has been little evidence of progressive renal disease.

Seven patients were found to have membranous glomerulonephropathy on initial biopsy. All 7 were living at final follow-up, an average of 44 months. None was found to have progressive renal insufficiency. All had serum urea nitrogen levels less than 20 mg. per 100 ml., and serial biopsy in 5 patients had revealed no significant change from initial biopsy.

Active Lupus Glomerulonephritis

The patients with this lesion have the worst prognosis. The lesions often progress and become more diffuse, even in spite of current therapy. This group typically has abnormal sediment, impaired renal function, high titers of antibodies, and low complement. If they respond to therapy, there may be regression and healing of the renal lesions, reduction of immunologic factors, and normalization of complement. On electron microscopy the proliferation and particularly the electron-dense deposits may disappear. Healing is also reflected in disappearance of immunoglobulin deposits in immunofluorescence studies.

Forty-seven patients were followed who, when studied initially, had active lupus glomerulonephritis. Only 15 were alive at final follow-up, an average of 34 months from initial study. Three of the 15 had elevated serum urea nitrogen levels (greater than 20 mg. per 100 ml.), one being

in frank renal failure (urea nitrogen 140 mg. per 100 ml.). Six had died of causes unrelated to renal disease; the remaining 26 had died of renal failure. The nephrotic syndrome was extremely common in this group. Five of 15 living patients had the nephrotic syndrome at some time during their illness. Nephrotic syndrome had occurred in 23 of 26 patients who had died from renal failure.

Patients with SLE and renal involvement therefore do not necessarily progress to renal insufficiency and death. Those with mild or minimal involvement or membranous nephropathy will, in all likelihood, have no progression. These patients are usually easily managed with little or no difficulty. Contrariwise, patients with lupus glomerulonephritis have a worse prognosis, and their management and successful treatment of their renal disease is a most difficult challenge to modern medicine.

MANAGEMENT OF LUPUS NEPHRITIS

The management of patients with SLE and renal involvement requires above all a cooperative patient and a dedicated, vigilant physician. An excellent monograph on the treatment of lupus nephritis has been published.⁴²

Before discussing the specific drug therapy of lupus nephritis it must be emphasized that auxiliary and more general therapeutic measures are often as important. They include avoidance of circumstances that tend to exacerbate preexisting disease. For many patients, exposure to sunlight, certain cosmetics, chemicals, or drugs will lead predictably to recrudescence of activity. When applicable, a thorough history of drug and chemical exposure, with appropriate restrictions, should be taken in all patients with SLE. Often forgotten are common items such as hair dyes and rinses, which can precipitate an acute attack.²⁰

Certain drugs are associated with lupus-like syndromes; the most notable at present are procainamide and hydralazine. Lee and Siegal have reported that 20 per cent of cases of SLE in New York may be directly related to these drugs.^{28, 29} These drugs should be avoided in patients with SLE.

Sufficient rest is of the utmost importance in the management of patients with SLE. Several investigators have commented on the relationship of clinical activity to physical activity, and the beneficial results of sufficient rest. The amount of rest needed is, of course, dependent on the individual case. Each patient should be encouraged to schedule his day to include sufficient periods of rest in order to avoid excessive fatigue.

The Use of Corticosteroids in the Management of Lupus Nephritis

Shortly after the introduction of steroids into the therapy of acute SLE, there were many reports of the excellent benefits. The benefit of

steroids in the therapy of lupus nephritis however was not clearly evident.

Muehrcke et al.,³⁸ in their study of 33 patients with SLE and renal involvement, reported that 22 had received steroids prior to renal biopsy and 11 had had no steroid therapy. Serial biopsies and clinical evaluation were made on 17 patients treated with corticosteroids, given in doses to suppress clinical symptoms. These doses did not exceed 200 mg. cortisone daily or its equivalent, and the average dose was 50 mg. cortisone daily. On subsequent biopsy studies, no patients were found to be improved, 4 had had no change, and 13 of the 17 were felt to have some progression of the renal lesion. It was concluded that no evidence of regression of structural damage to the kidney following treatment with cortisone could be found.

In 1961, however, Pollak et al.⁴¹ reported the effects of large doses of prednisone on lupus glomerulonephritis. They had noted regression of renal damage in a patient whose systemic symptoms required 150 to 300 mg. cortisone daily for 6 months, and a larger study was undertaken. Sixteen patients with active lupus glomerulonephritis were subsequently treated with large doses of prednisone—an average of 47.5 mg. daily for 6 months—followed clinically and histologically by renal biopsy. Detailed comparison of 10 patients treated with low doses of steroids with the 16 patients treated with high doses demonstrated the beneficial effects of high-dosage steroid treatment. Whereas all 10 in the low-dosage group had died, on an average of 13.8 months after the initial study, only 7 of 16 patients on high-dosage therapy had died. The other 9 had survived for an average of 34.2 months after first being studied. Histologic analysis of initial biopsies revealed similar severity and activity initially in both groups. Serial biopsies, however, showed progression in the low-dosage group, whereas in the high-dosage group the active lesions had disappeared or decreased in most patients.

Of those patients treated with high doses of steroids, 5 had blood urea nitrogen levels greater than 30 mg. per 100 ml. initially, and all had died. In 11 patients the blood urea nitrogen was less than 30 mg. per 100 ml. initially; 9 were alive and not in renal failure at follow-up.

A further follow-up by the same investigators of a total of 87 patients revealed more clearly the natural history of renal involvement in lupus and the response to steroid therapy.⁴⁵

The previous observations that long-term high dose steroid therapy altered the activity and progression of the renal lesions were confirmed in the analysis of the 47 patients with active lupus glomerulonephritis. Sixteen patients had been treated with low doses of steroids. Of this group, 13 had died in renal failure, 2 had died of nonrenal causes, and only 1 was alive. Serial histologic studies of 13 of the 16 patients in the low dosage group had shown that the renal lesions became more severe and histologic activity persisted.

Thirty-one patients were deliberately treated with large doses of prednisone (40 to 60 mg. for 6 months), and serial histologic study made six months after treatment started.

Of the 31 patients in this group, 13 had died of renal failure and 4 of

nonrenal causes, and 14 patients were alive at final follow-up. Only one was in renal failure; the remainder had serum urea nitrogen levels less than 25 mg. per 100 ml.

Serial histologic examination showed less rapid progression of severity and decrease in activity of the lesions in the group treated with high doses of prednisone.

It was again noted, as in the previous study, that large doses of steroid were relatively ineffective when serum urea nitrogen exceeded 30 mg. per 100 ml. before treatment. Despite high doses of steroids in 10 patients with serum urea nitrogen values above 30 mg. per 100 ml., only 2 survived, 1 being in renal failure at follow-up.

The beneficial effects of high-dosage long-term steroid therapy have been confirmed by other investigators^{18, 62}

It is clear that there is a spectrum of renal involvement in lupus ranging from no involvement to severe active glomerulonephritis. The studies of Pollak et al.⁴⁵ have shown that progression of renal involvement to renal failure, or the development of active lupus glomerulonephritis in those patients initially found to have normal kidneys, minimal involvement, or membranous nephropathy, is distinctly uncommon. In general these groups will have long-term survival rates and will need therapy as determined by clinical symptoms. On the other hand, progressive renal failure seems to be the rule in those patients with active lupus glomerulonephritis. High-dosage steroid therapy has been shown to be effective in those patients who, on initial evaluation, do not have serum urea nitrogen levels exceeding 30 mg. per 100 ml. or other evidence of renal functional impairment. Gary et al.¹³ have reported on renal function after prolonged survival of patients with lupus glomerulonephritis.

Nitrogen Mustard and Other Immunosuppressive Agents

The failure of high doses of steroids in some patients with active lupus glomerulonephritis has led to investigation of other modes of therapy. As the underlying pathophysiology of lupus nephritis has become clearer, many investigators have approached the therapy of lupus nephritis in terms of abrogating the immune response of the patient. This has led in recent years to several reports on the usefulness or uselessness of many so-called immunosuppressive agents.^{1, 5, 14, 32, 36, 52}

In fact, however, nitrogen mustard, an alkylating agent, was first used in the therapy of glomerulonephritis in 1949. Since then, several reports have demonstrated the beneficial effect of nitrogen mustards in lupus nephritis.^{7, 9, 22, 51} The majority of patients given mustards were not responsive to steroid therapy. Dubois⁹ reported that 39 (78 per cent) of 50 patients had some beneficial effects. Dillard et al. recently reported their results comparing high dose steroids and steroids plus nitrogen mustard in patients with active lupus glomerulonephritis. Thirty-one patients had high doses of steroids only, and 12 patients had high doses of steroids plus a course of nitrogen mustard. Thirteen of 31 treated only with steroids died. Four of 12 who had combined therapy died. The other 8 were alive with average survival of 39.5 months after

treatment was started. Careful histologic analysis of several biopsies in both groups revealed that no patient receiving combined therapy had shown progression in severity or activity of the disease. In comparison, 3 patients on high-dosage steroids had shown progression in severity, and 4 had persistent activity after 6 months of treatment. Among the 8 patients that were surviving after combined treatment, 6 had inactive disease clinically; 5 were able to have steroid doses decreased to lower levels, and 3 of these were able to be taken off of steroids completely.

We have also used nitrogen mustard in severe cases of lupus glomerulonephritis, especially in patients resistant to steroids, or where side-effects were prohibitive. Our experience has been that mustards are of benefit in many cases of active lupus glomerulonephritis.⁵¹

The method of administering nitrogen mustard that we have used has been well tolerated, with a minimum of side reactions and toxicity. A standard course of 0.4 mg. per kg. is divided into three doses. The drug is given intravenously at bedtime on three successive nights after the patient has received a sedative and an anti-emetic preparation. Local discomfort and phlebitis are minimized by the infusion of a liter of fluid at a fairly rapid rate following injection of the nitrogen mustard. Nausea and vomiting do occur, but this has not been a serious problem. The white blood count should be followed for a period of about 2 weeks, since there is usually a transitory leukopenia. No serious reactions have occurred in our series.

A second or further course can be given after an interval of about 6 weeks.

There have been sporadic reports of the use of other alkylating agents in the treatment of SLE and, occasionally, lupus nephritis.^{14, 52} The results have been uneven, and the use of agents such as cyclophosphamide must be regarded as experimental.

Antimetabolic agents, such as 6-mercaptopurine, 6-thioguanine, methotrexate, and azathioprine have also been used in lupus nephritis, especially in steroid-resistant cases. Although some reports appear to show beneficial effects in some cases, the concomitant use of steroids and the nonconformity of cases make it difficult to accurately evaluate their effectiveness.

Recently a drug which inhibits protein synthesis, related to the antibiotic chloramphenicol, has been used in the therapy of lupus nephritis. Thiamphenicol (Thiocymetin), the methylsulfonyl analogue of chloramphenicol, has been shown to decrease antibody synthesis and prevent the development of heterologous nephrotoxic nephritis.^{60, 61} These findings have led to its use in lupus glomerulonephritis, and preliminary reports have shown evidence of suppression of immunologic injury as reflected by decreases in antinuclear antibody titers, increase in serum complement, and disappearance of gamma globulin in the glomeruli.^{56, 59}

The most hopeful observation that has been made is that sustained remissions lasting from 9 months to 3 years have been obtained following a single 16 day course of therapy.⁵⁹

We are presently engaged in a study of the efficacy of this drug in

lupus nephritis, and although our numbers of subjects are few and follow-up is short, we have evidence of good immunosuppression in several patients, as demonstrated by dramatic falls in antinuclear antibody titers. Further studies with this promising agent are certainly needed.

We, as have others, have used the B₁C titer or whole complement titer as an index of active renal involvement, and find it useful to monitor patients in remission. As pointed out by Schur and Sandson,⁵⁰ a decrease of serum complement titer of greater than 50 per cent is invariably associated with an exacerbation of renal involvement and often precedes other clinical signs of activity. It may soon be feasible to have even more precise indications of immunologic activity, such as free DNA or DNA antibody titer, as standard laboratory procedures, but for the present serum B₁C levels or whole complement are very useful. It there are serologic indications of exacerbations, prednisone or other medication should be raised to a high level and the patient followed closely for clinical indications of active disease.

IN SUMMARY

There are some general principles that one can follow in the management of lupus nephritis.

First, the physician must have a high index of suspicion of renal involvement in any patient with SLE. The diagnosis of renal involvement should be confirmed with a renal biopsy for accurate assessment of the degree of involvement and a clearer prognosis.

When biopsy reveals no involvement, minimal involvement, or membranous changes only, therapy is directed toward control of clinical signs and symptoms. Urinalysis and simple tests of renal function should be repeated at intervals to detect any progression of renal involvement. The B₁C titer or whole complement activity should also be determined at intervals for evidence of disease activity.

In the instances in which initial biopsy reveals active lupus glomerulonephritis and in which renal function is well preserved (BUN less than 30 gm. per 100 ml.) high doses of prednisone (40 to 60 mg. daily) for 6 months are recommended. During this interval, urinalysis, proteinuria, and renal function should be followed as parameters of improvement. At the end of the course of therapy, a renal biopsy should be assessed for histologic changes. If the renal lesion is still active and clinically the patient still demonstrates severe involvement, a course of nitrogen mustard treatment is recommended.

When initial evaluation and renal biopsy reveal severe involvement and compromised renal function, our present mode of treatment consists of high doses of steroids for 4 to 6 weeks, with close observation of urinalysis, proteinuria and renal function, and B₁C titers for signs of improvement. If there appears to be little or no improvement, we recommend a course of nitrogen mustard followed by high doses of steroid. In many critically ill patients nitrogen mustard may be given at the outset.

In cases in which steroids or nitrogen mustards or both have not had a beneficial effect, we are presently investigating the efficacy of thiamphenicol (Thiocymetin). Our preliminary observations are that there has been good evidence of immunosuppression, but full evaluation of beneficial effects await further studies.

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Viruses and the Kidney

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The possible role of viruses in the pathogenesis of human renal disease has been the subject of few reviews and much speculation.^{56, 63, 72} Since most forms of renal disease are idiopathic, the identification of an etiologic agent such as a virus may permit a preventive therapeutic approach to the problem of end-stage renal disease. However, the consideration of viruses as possible etiologic agents has been overshadowed by emphasis on the role of streptococcal infection and immune mechanisms in the pathogenesis of acute glomerulonephritis. In addition, the difficulties inherent in virus isolation and identification have hampered a clinical investigational approach to the possible association of viruses and kidney disease. Although many laboratory animal models of virus-induced renal disease have been established, obvious difficulties in equating morphological and biological changes in different species have limited the usefulness of animal experimentation in this field.

The purpose of this review is to summarize the reported cases of clinical viral infection associated with manifestations of renal disease in man and to consider some experimental animal models of virus infection which might be fruitful in delineating possible pathogenetic mechanisms in human kidney disease.

Most of the reports involving virus and kidney describe the occurrence of signs and symptoms of renal disease during the course of acute viral infections (Table 1). For the purpose of this review, the types of renal disease described in these reports can be grouped into three categories: (1) transient renal abnormalities associated with acute systemic viral infection; (2) severe progressive renal disease associated with acute viral infection; and (3) renal diseases in which viral infections have been suspected but not firmly associated.

Transient Renal Abnormalities with Acute Systemic Viral Infections

Although there are isolated reports implicating practically all systemic viral infections in the development of transient alterations in

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Table 1. *Renal Manifestations Associated with Common Acute Virus Infections*

VIRUS	CLINICAL MANIFESTATIONS	RENAL MANIFESTATIONS	REFERENCES
Mumps	Parotitis	Viruria	94,96,97
		Hematuria, proteinuria	52,92,97
		Decreased creatinine clearance	92,97
		Fatal necrotizing Glomerulonephritis	52
		Paroxysmal cold hemoglobinuria	16
Coxsackie B ₃	Aseptic meningitis	Viruria	50,93,95
		Decreased PSP excretion	93
Coxsackie B ₄	Pancarditis	*Focal glomerulonephritis and interstitial nephritis	11
ECHO-6	Aseptic meningitis, pharyngitis, myositis	Hematuria, proteinuria	67
ECHO-9	Aseptic meningitis, pharyngitis, myalgia	Hematuria, proteinuria	82, 102
		Acute proliferative glomerulonephritis*	102
Adenovirus 3,4	Pharyngoconjunctival fever	Hematuria	98
Adenovirus 7a	Fatal pneumonia (infants)	Focal glomerulonephritis*	14
Vaccinia	Primary vaccination	Diffuse necrotizing glomerulonephritis*	83
	Revaccination	Diffuse glomerulonephritis* Acute tubular necrosis	44 27
	Eczema vaccinatum	Viruria	8,35
	Multiple vaccinia lesions		
Cytomegalovirus	Asymptomatic or cytomegalic inclusion disease in infants and children	Viruria Diagnostic inclusions in urinary sediment Viruria	81,100
	Adult cytomegalo- virus infection (immunosuppression)	Viruria	79
Measles	Exanthem	Viruria	34
		Viral antigen in urinary sediment	65
Infectious hepatitis	Hepatitis	Proteinuria and hematuria Focal proliferative glomerulonephritis	19

Renal biopsy diagnosis.

urine sediment or protein, only infections with mumps, Coxsackie, and ECHO viruses have firmly been associated with repeated instances of renal disease. Viruria has been repeatedly demonstrated during the first 14 days of mumps parotitis.^{94, 96, 97} During the same period, microscopic hematuria and proteinuria occurred in many of the patients, and 85 per cent of tested patients had a mild transient decrease in creatinine clearance.^{92, 97} With the exception of two children with a fatal nephropathy associated with mumps virus infection⁵² and a single case of paroxysmal cold hemoglobinuria following typical mumps parotitis,¹⁶ all the reported cases have been without apparent renal sequelae.

Coxsackie B viruses have been isolated from the urine during clinical infection characterized by aseptic meningitis and myalgia.^{50, 93, 95} Specific Coxsackie B-5 viral antigens have been demonstrated by immunofluorescence in exfoliated cells in the urinary sediment in six of 12 patients with aseptic meningitis.⁴⁶ In most reported cases, there was no mention of proteinuria or hematuria. Depression in PSP excretion in one case was the only manifestation of abnormal renal function.¹¹

A recent case of Coxsackie B-4 viral pancarditis was attended by persistent hematuria, albuminuria, and progressive deterioration of renal function. At autopsy, focal glomerulonephritis with interstitial nephritis was associated with Coxsackie B-4 antigen within the glomeruli and interstitium, as demonstrated by immunofluorescence.

ECHO type 9 infection, like Coxsackie B viral infection, is also a cause of aseptic meningitis. In an epidemic in Milwaukee in 1957, nearly 50 per cent of the patients had microscopic hematuria and 10 per cent had significant proteinuria occurring transiently during the febrile illness.⁸² Two cases of acute glomerulonephritis associated with ECHO 9 virus have been reported.¹⁰² Renal biopsy in one patient revealed a proliferative glomerulonephritis. In a recent epidemic of aseptic meningitis, pharyngitis and myalgia due to ECHO type 6 virus infection, one patient had proteinuria and hematuria but recovered in 5 days with no residual renal disease.⁶⁷

Adenoviruses have also been associated with transient manifestations of renal disease. In an epidemic of pharyngoconjunctival fever caused by types 3 and 4 adenovirus, many patients had pronounced hematuria.⁹⁸ In a report of 27 cases of pneumonia in infants and children due to adenovirus type 7, five patients were considered to have signs of acute glomerulonephritis.¹⁴

Vaccinia virus infection, typically following vaccination for smallpox, has rarely been associated with the development of renal disease. One case of a fatal glomerulonephritis has been reported following revaccination, but because of a long latent period, was considered to be an allergic manifestation rather than the result of direct viral involvement of the kidney.⁴⁴ The development of acute diffuse glomerulonephritis after primary vaccination has also been recorded, as has acute tubular necrosis occurring 9 days after vaccination.^{27, 83} Vaccinia virus has been isolated from the urine of children with multiple cutaneous vaccinal lesions and patients with eczema vaccinatum.^{8, 35}

Infectious hepatitis has also been accompanied by transient manifestations of renal involvement.¹⁹ During an outbreak of hepatitis among troops in Korea, careful renal studies in 20 consecutive patients revealed

significant proteinuria in 10 and hematuria in 8. Renal biopsies demonstrated focal proliferative glomerular changes, basement membrane thickening, and collapse of some capillary loops. However, in none of these patients was there evidence of residual renal disease.

Although other virus infections have been reported to result in alterations of the urinary sediment and viruria, no other clinical manifestations of renal disease were noted.^{9, 30, 31, 36} Measles virus has been cultured from the urine,³⁴ and the demonstration of measles virus antigen in epithelial cells within the urinary sediment has been suggested as a rapid diagnostic procedure for identification of measles even during the prodromal stage.⁶⁵ Cytomegalovirus infection deserves special notice because the identification of characteristic inclusion-bearing epithelial cells in the urinary sediment has served as a useful tool in diagnosis of the disease in infants and children.¹⁰⁰ Also of importance is the high incidence of cytomegalovirus infection of transplanted kidneys in patients on immunosuppressive therapy.⁷⁹ However, despite the presence of prolonged and persistent viruria, and virus in tubular epithelial cells with occasional foci of interstitial nephritis, no renal functional derangement has been attributed to cytomegalovirus infection.⁸¹

Progressive Renal Failure Associated with Acute Viral Infection

Although isolated cases of mumps,⁵² Coxsackie,¹¹ and Vaccinia^{27, 44} virus infections have been rarely related to rapidly progressive renal disease, only the arthropod-borne viruses of epidemic hemorrhagic fever are regularly associated with the development of renal failure. Hemorrhagic fever with a renal syndrome first came to the attention of the American medical profession in 1951, during the Korean conflict.⁸⁹ The clinical course was characterized by a febrile phase of 3 to 8 days, an oliguric phase, and finally, with recovery, a diuretic phase.²⁶ Severe proteinuria and hematuria preceded the development of renal shutdown. Thrombocytopenia, leukocytosis, and marked increase in capillary fragility occurred during the febrile period. Renal biopsy and autopsy revealed acute tubular necrosis with hemorrhage, characteristically limited to the corticomedullary junctional zone.⁷⁵ Those patients who survived, regained normal renal function with no apparent sequelae. A similar disease caused by closely related arboviruses, with hemorrhagic fever and acute renal shutdown, has been described in epidemic form in Bolivia⁹¹ and Argentina,⁸⁵ and is endemic in the Far East and the Soviet Union. Arbovirus infections with sporadic cases of hemorrhagic fever with renal involvement have been a major medical problem among troops in Vietnam.²⁰

Other than the arboviruses causing hemorrhagic fever, there are no viruses which are classically nephrotropic in man or are recognized as direct causative agents in the development of renal disease. However, there are specific renal syndromes which are suspected of being associated with viral infections.

Renal Diseases in Which Viral Association is Suspected

The syndrome consisting of pulmonary hemorrhage and progressive glomerulonephritis was originally described in a patient with influenza

by Goodpasture.³³ Although the agent responsible for influenza was unknown in 1919, Goodpasture suggested that a virus of influenza may persist in the body for 6 weeks, with the production of pulmonary and renal lesions. Although the association of a virus infection with the development of subsequent hemoptysis and renal failure remains unproven, others have commented on the precedent history of respiratory infection in Goodpasture's syndrome.⁶ In our own material, two of four patients with hemorrhagic lung-renal syndrome had precedent histories of "flu-like" illnesses 3 weeks and 7 weeks prior to the development of hemoptysis. Since Goodpasture's syndrome is associated with the development of autoantibodies directed against lung and glomerular basement membrane,^{60, 69} it has been suggested that a virus is responsible for alteration of self-antigens, so that they are recognized as foreign and induce the production of antibody.²³ However, no evidence has yet emerged to support this hypothesis.

The hemolytic-uremic syndrome is an illness occurring principally in infants and children which is characterized by thrombocytopenia, hemolytic anemia, and acute renal disease.²⁸ The frequent association of the onset of this syndrome with respiratory and gastrointestinal infections and the occurrence of the syndrome in small epidemics has suggested a possible etiologic association with an infectious agent.

Virological studies have resulted in the isolation of a virus, probably of the arbovirus group, from an epidemic of the hemolytic-uremic syndrome in Argentina,²⁹ and one of the Coxsackie virus group A type 4 from an infant with the syndrome in the United States.³² However, other attempts at virus isolation have been unsuccessful.⁵⁴ Recently, a rickettsial organism was isolated from two children with the hemolytic-uremic syndrome and from one adult with thrombotic thrombocytopenic purpura.⁷¹ The organism appeared to be transmitted by mites, and inoculation of the rickettsia into rhesus monkeys resulted in anemia and thrombocytopenia. Deposition of fibrin in glomerular capillaries related to a hypercoagulability state has been incriminated in the pathogenesis of the hemolytic-uremic syndrome.⁶⁴ Since it has been shown that various viral agents can induce intravascular coagulation, it is likely that many viruses as well as chemicals may be responsible for induction of this syndrome.⁶⁸

There have been occasional well-documented reports of acute glomerulonephritis unassociated with a streptococcal infection. Bates et al. described 10 patients with acute diffuse proliferative glomerulonephritis, confirmed by renal biopsy, in whom a preceding streptococcal infection could not be ascertained on clinical or serological grounds.⁴ Clinically, there was a suspicion of a virus infection in most of these cases, but viral studies were not performed. In cases of acute recurrent glomerulonephritis unassociated with streptococcal infection, there was a history of transient episodes of hematuria occurring during epidemics of upper respiratory infections.¹⁰¹ In one such series of 9 patients with recurrent hematuria, pharyngitis and upper respiratory infections were invariably associated with the exacerbations.⁸⁰ Renal biopsies showed a focal proliferative glomerulonephritis, and follow-up studies revealed the course to be nonprogressive and benign. In a similar series, influenza virus was implicated in the exacerbations of hematuria and proteinuria.¹

SIGNIFICANCE OF ASSOCIATED VIRUS AND RENAL DISEASE

Although microscopic lesions have been observed in renal biopsies of patients with mumps, Coxsackie, and ECHO virus infections, and viruria even in the absence of viremia, has been demonstrated in most systemic viral infections, the exact cause of the clinical manifestations of renal disease in these cases is unknown. Abnormal results of urine analysis and transient alteration of renal function, particularly with mumps virus infection, have suggested to clinicians that the viruria is due to replication of the virus within cells of the kidney. However, viruria could also be the result of filtration from the blood and concentration of virus in the urine with uncoupling of virus from circulating neutralizing antibody, in which case the virus could be isolated from the urine but not the blood.

Alteration in glomerular permeability with resultant proteinuria may be due to the effects of by-products of a virus infection on the kidney rather than direct cytopathic viral effects on kidney cells. Such a mechanism would seem likely particularly with a myxovirus infection such as mumps. Myxoviruses contain the enzyme neuraminidase which has the ability to split sialic acid from glycoproteins. The glomerular basement membrane has a high content of glycoprotein,³⁰ and neuraminidase has been shown to induce alteration in the mouse glomerulus following experimental administration of the enzyme.⁴⁰

Glomerular changes with mild proteinuria have also been reported to occur experimentally with extra-renal foci of inflammation.⁶⁶ Perhaps the transient abnormalities in urinalysis in patients with parotitis or aseptic meningitis are due to a similar indirect mechanism of renal involvement. Even with hemorrhagic fever and the associated renal tubular necrosis, the damage to the kidney may be secondary to increased vascular permeability and hypovolemia rather than to direct involvement of the kidney by the virus.³⁷ However, the rare occurrence of progressive and fatal glomerulonephritis with mumps and Coxsackie viruses seems to indicate that some viruses can directly involve the kidney and induce acute renal disease either by multiplication within the renal glomerular and tubular cells or by participation in the formation of antigen-antibody complexes and the subsequent development of immune complex glomerulonephritis.

In searching for viral agents in renal disease, attempts at isolation of virus from the urine of patients with chronic glomerulonephritis and from 79 consecutive renal biopsies were uniformly unsuccessful.^{55, 84} However, even in cases in which virus had been successfully isolated from kidneys of children with virus diseases, the virus was obtained only by establishing viable kidney cells in tissue culture and, in most cases, could not be isolated from suspension of renal homogenates.⁷

Perhaps the more rational but less direct method of attempting to implicate virus in human renal disease is through the use of specific immunofluorescence. Burch and his co-workers have recently reported the demonstration of Coxsackie B-4 virus antigen in 11 kidneys from 104

consecutive autopsies.¹² Eight of the kidneys showing immunofluorescence had histological evidence of pyelonephritis, and one had glomerulonephritis, suggesting that some forms of renal disease may be caused by the direct action of Coxsackie virus.

In our own laboratory, we have investigated the renal effects of acute virus infection using the murine strain of cytomegalovirus (MCMV). Inoculation of young mice with homogenates of infected salivary glands, depending on the dose of virus, resulted in either a fatal necrotizing hepatitis or a non-fatal generalized infection.¹¹ With sublethal doses, typical viral inclusions were observed within the renal glomeruli by the fifth day following infection (Figure 1). From the third to the tenth day, all infected mice had significant proteinuria. Electron microscopy of involved glomeruli revealed virus only within glomerular mesangial cells (Figures 2 and 3), accompanied by partial occlusion of glomerular capillaries by cytomegalic expansion of mesangial cells. Although MCMV was isolated from the urine and from homogenates of kidney during the first 6 days, no virus could be recovered from renal tissue after the seventh day of infection.

In preliminary experiments utilizing indirect immunofluorescence for identification of MCMV antigen in the mouse kidney, viral antigen was observed in glomeruli for a period of up to 5 weeks following the experimental infection. However, despite this persistence of antigen, no chronic renal disease has as yet been observed in these animals. Similar persistence of viral antigen in glomeruli was reported to occur for up to 8 weeks following experimental Coxsackie B virus infection of mice.¹⁰

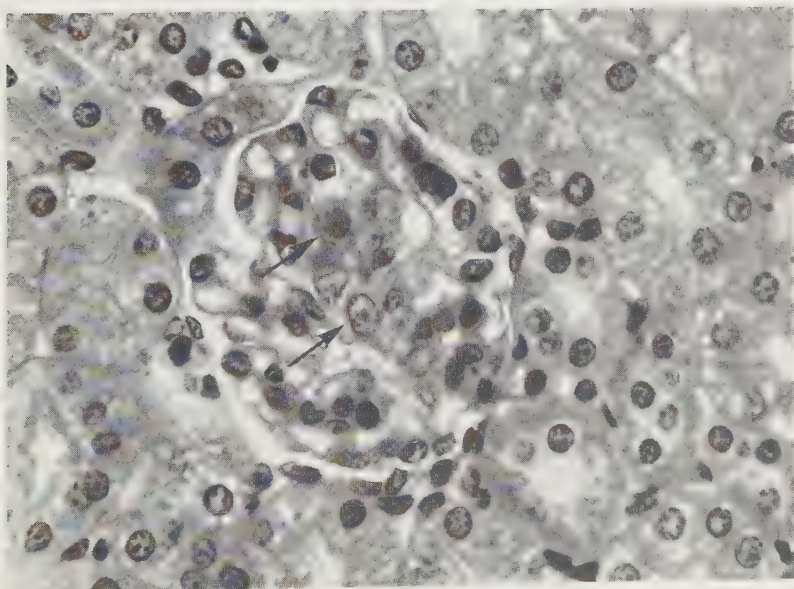


Figure 1. Micrograph of mouse glomerulus 5 days after inoculation with murine cytomegalovirus (MCMV). Note the characteristic intranuclear inclusions (arrows) within cytomegalic mesangial cells. (Hematoxylin and eosin; $\times 540$.)

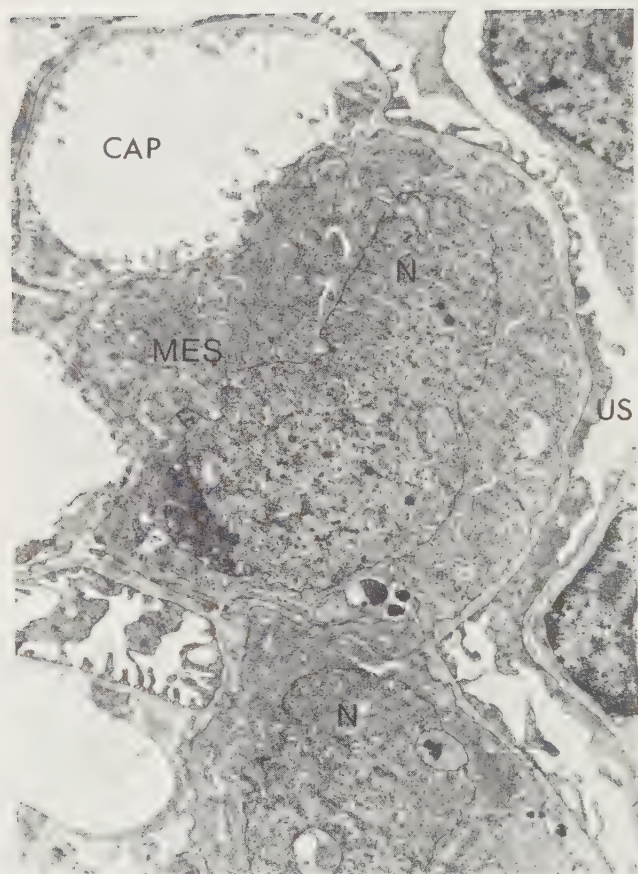


Figure 2. Electron micrograph of mouse glomerulus 5 days after inoculation with murine cytomegalovirus. The mesangial cells (MES) are greatly enlarged, partially compromising the capillary lumen (CAP) and bulging toward the urinary space (US). Numerous virus particles are present within the nucleus (N). (Lead citrate and uranyl acetate stain; $\times 4800$.)

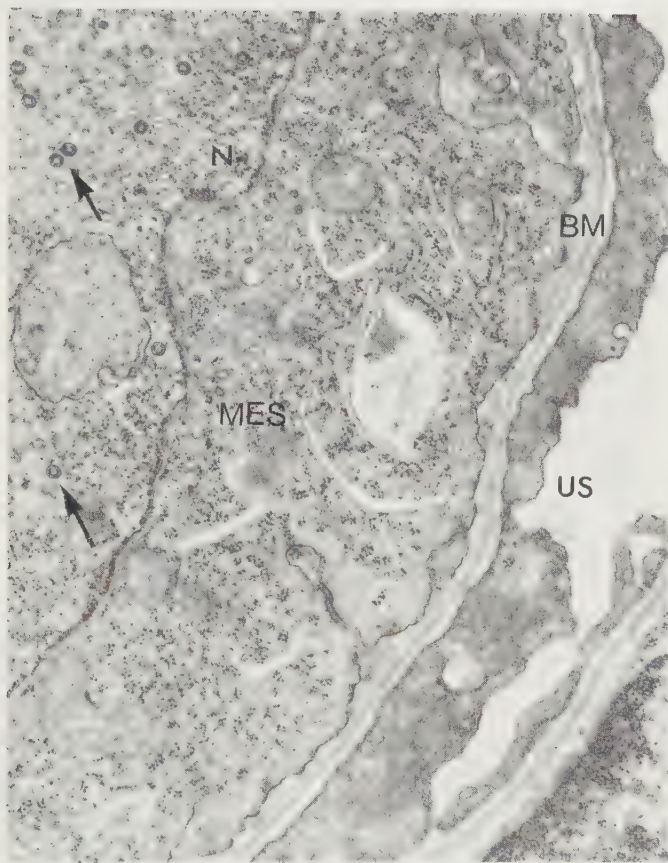


Figure 3. Electron micrograph of mouse glomerulus 5 days after inoculation with murine cytomegalovirus. Virus particles (arrows) are present within the nucleus (N) of the mesangial cell (MES); urinary space (US); basement membrane (BM). (Lead citrate and uranyl acetate stain; $\times 23,000$.)

Although the demonstration of antigen in these experimental models and the finding of Coxsackie antigen in human kidney obtained at autopsy suggests that persistence of viral antigen following acute infection may be implicated in the later development of renal disease,¹² more extensive survey of renal biopsies with virus specific fluorescent antibody is required to establish the importance of these observations.

Experimentalists have diligently searched for animal models of renal disease with morphological and biological similarities comparable to human glomerulonephritis. Three such models are worthy of note inasmuch as they exemplify a pathogenic sequence which might have a role in the development of some forms of glomerulonephritis in man.

ANIMAL MODELS OF RENAL DISEASE

Lymphocytic Choriomeningitis (LCM) Virus in Mice

Hotchin and Collins first reported the development of a chronic disease in mice persistently infected with LCM virus.¹⁸ Whereas inoculation of mature and immunologically competent mice with the virus resulted in fatal meningitis, spontaneous congenital infection or inoculation of immature newborn animals resulted in persistent viremia and the development of progressive chronic glomerulonephritis in later life.

Although the relationship of persistent infection to the immunological status of the animal has not been entirely clarified, the development of persistent viremia has been attributed to a split-tolerance, implying a non-recognition of LCM antigen by cell-mediated but not antibody-mediated immune responses.^{17, 99} Persistently infected animals produced large amounts of anti-LCM antibody, which formed virus-antibody complexes that localized in the renal glomeruli.⁷³ The passive entrapment of non-toxic antigen and antibody complexes along with serum complement within the glomerular filter has been shown to elicit a phlogogenic response resulting in glomerulonephritis.²² With LCM infection, circulating and tissue-fixed virus-specific antibodies have been identified, and the increasing content of viral antigen and antibody in the kidney with age has been associated with the progressive development of fatal renal disease.⁷⁴

With human glomerulonephritis of various types, immune complexes have been localized within the diseased glomeruli.⁵⁹ In some instances such as serum sickness²¹ and poststreptococcal glomerulonephritis⁵⁷ the antigens have been at least partially identified, but in most other forms of immune-complex disease, the nature and origin of the antigens are entirely unknown. As yet, there have been no reports of viral antigens associated with immune-complex human glomerular disease, although the LCM model suggests that such an association may occur. The search for viral antigens in human disease would seem especially indicated in cases of chronic glomerulonephritis associated with persistent hypocomplementemia and the presence of IgG and B₁C within glomeruli.⁴⁵

Aleutian Disease of Mink

Aleutian disease is a common and economically important spontaneous disease of one strain of mink characterized by proliferation of plasma cells, hypergammaglobulinemia and a progressive glomerulonephritis.³⁷ The pathogenesis of the renal changes in mink with aleutian disease is of particular interest because the changes are initiated by a virus and the glomerular lesions closely resemble the lesions seen in some human diseases such as systemic lupus erythematosus.^{42, 43}

As with LCM infection, virus-antibody complexes have been identified in the serum of affected animals, and viremia persisted until death.⁷⁸ Furthermore, immunofluorescent studies of the involved glomeruli exhibited deposits of B₁C and IgG and suggested that the virus-antibody complexes passively filtered out in the glomeruli in a manner similar to that which occurs in LCM infection.⁴³ However, a second possible source of antigen-antibody complex in aleutian disease was identified as circulating DNA and anti-DNA antibodies. Both DNA antigens and antinuclear antibodies have been shown to occur in mink with aleutian disease.³

Systemic Lupus Erythematosus (SLE) in NZB Mice

The discovery of serologic abnormalities and nephritis in the New Zealand black inbred mouse provided a laboratory model of striking analogy to human systemic lupus erythematosus (SLE).³⁹ When the NZB mice were cross-bred with NZW or other inbred strains, hemolytic anemia and glomerulonephritis developed in the aging offspring.³⁸ Sex had an important influence on the incidence and course of the renal disease, with 98 per cent of female mice dying before 1 year of age.¹³ The involved mice had positive LE cell preparations, and the development and prognosis of the glomerulonephritis was closely related to the formation and titer of circulating anti-nuclear antibodies.⁶² The histopathological and ultrastructural evolution of the glomerular lesions were almost identical to those seen in human SLE and immunopathological studies revealed complement and immune globulins within the affected glomeruli analogous to findings in lupus nephritis of man.¹⁷ In addition, immunochemical assay of the globulins in the mouse kidney revealed specificity for DNA,⁶² a finding similar to that reported in human SLE.⁶¹

Unlike LCM infection in mice and aleutian disease in mink, evidence implicating virus in the development of the renal lesions in NZB mice is scant. The transmissibility of renal disease by cell-free filtrates from affected mice strongly suggested that the disease is mediated by a viral agent.⁷⁰ The striking similarity of the morphological and serological changes in these mice with human SLE and the implication of genetic association and possible viral transmission dictates a need for further investigation of this animal model.

PERSISTENT AND LATENT INFECTION IN MAN

There now seems little reason to doubt the existence of diseases in man related to persistent or latent viruses. Attention was first drawn to

persistent virus infection by Sigurdsson and his co-workers, who described a "slow" virus infection in sheep.⁸⁷ Slow virus infections have been characterized in part by the persistence of high titers of virus within the host and the subsequent development of immunologically mediated disease, such as glomerulonephritis, as seen in LCM virus infection of mice.⁴⁹ Although a persistent or slow virus infection resulting in disease has not as yet been conclusively demonstrated in man, various diseases of the central nervous system in animals have been related to slow virus infections.²⁴ That viruses can persist in man in the presence of high levels of neutralizing antibody is exemplified by the common recrudescence of herpes simplex virus lesions of the lips and the demonstration of persistent virus excretion for periods as long as 2 years following congenital infections with rubella and cytomegaloviruses.^{2, 81}

During the last 5 years, latent viruses have become increasingly implicated in the pathogenesis of human diseases, particularly of the central nervous system. The initial observation of virus-like structures within the degenerating neurons from patients with subacute sclerosing panencephalitis was shortly followed by the demonstration of measles virus antigen within the cells and finally by the isolation of measles virus from cultures of affected brain.^{5, 18, 76} Myxovirus-like filaments similar to measles virus have been observed by electron microscopy in muscle from a patient with polymyositis and in various tissues from patients with SLE.^{15, 25, 53, 58}

In a report from our laboratory,⁸⁸ electron microscopy of a renal biopsy from a 58 year old man with idiopathic nephrotic syndrome revealed paramyxovirus-like filaments within glomerular endothelial cells (Fig. 4) and virus-like particles morphologically similar to mumps virus within the glomerular basement membranes (Fig. 5). Although neither infectious virus nor viral antigen could be demonstrated in tissue from a subsequent renal biopsy, complement fixation titers of mumps antibody in the patient's serum suggested the possibility of a recent or active mumps virus infection. Similar serological studies in patients with SLE have demonstrated significantly elevated titers of antibody to measles and parainfluenza viruses.⁷⁷ Antibodies to double-stranded RNA, probably of viral origin, have also been demonstrated in patients with SLE.⁸⁶ These observations tend to further incriminate persistent virus infection in some forms of renal disease.

Isolation of persistent or latent viruses requires special handling and long-term cultivation of the tissue suspected of harboring the latent virus. In a survey study of over 400 cultures originating from monkey kidney cells used for vaccine development, 50 per cent of the cultures were found to contain latent viruses only after prolonged observation for periods of many months.⁵¹ Recovery of measles virus from a patient with subacute sclerosing panencephalitis necessitated 15 subcultures and 5 months of manipulation of tissue culture originating from affected brain.⁷⁶ Similar prolonged cultivation of normal kidney tissue as well as kidney from patients with renal disease will probably be required for identification of a latent virus that may have some role in the genesis of renal disease.

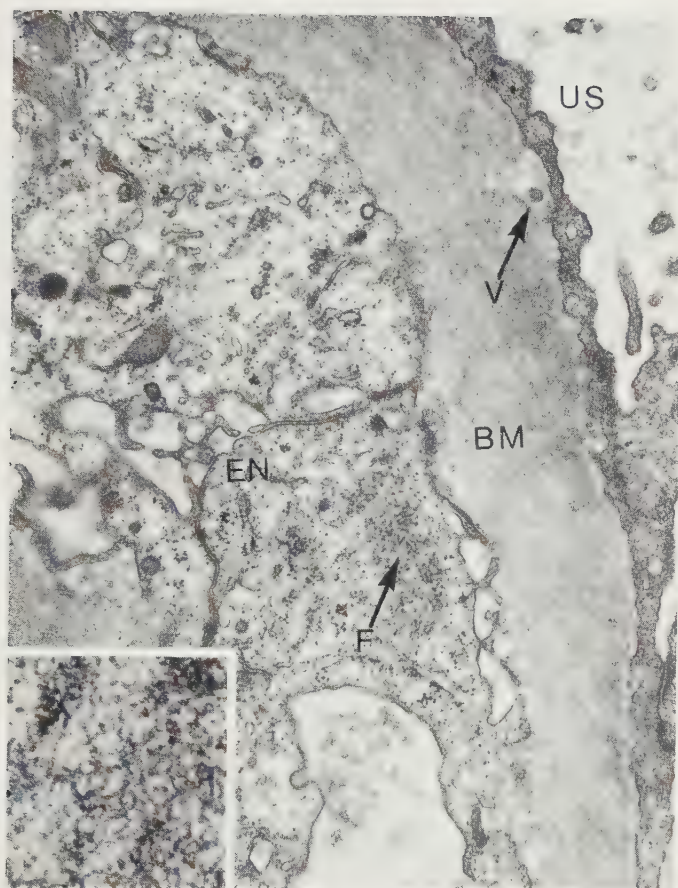


Figure 4. Electron micrograph of a glomerulus from a renal biopsy of a patient with proteinuria. Virus-like filaments (F) were found within glomerular endothelial cells (EN), and virus-like particles (V) were observed within the basement membrane (BM); urinary space (US). (Lead citrate and uranyl acetate stain; $\times 25,000$. Insert ($\times 56,000$) shows filaments in greater detail.)



Figure 5. Electron micrograph of a glomerulus from a renal biopsy of a patient with proteinuria. Virus-like particles (V) having size and structure similar to paramyxovirus were found underlying the epithelial foot-processes (EP) within the glomerular basement membrane (BM). (Lead citrate and uranyl acetate stain; $\times 96,000$.)

CONCLUSIONS AND SUMMARY

Acute systemic virus infections, particularly with mumps, Coxsackie and ECHO viruses are occasionally associated with transient manifestations of renal involvement but rarely attended by the development of glomerulonephritis. Although it is unlikely that acute virus infections are a major immediate cause of renal disease, the frequent association of recent virus infections with Goodpasture's syndrome, recurrent hemorrhagic glomerulonephritis and the hemolytic-uremic syndrome obligates detailed virologic studies of these conditions. Persistence of viral antigen in the kidney following experimental infection with Coxsackie and cytomegaloviruses suggests a possible delayed role for viruses in the genesis of chronic glomerulonephritis. Binding of specific antibody and complement by viral antigen persisting within the glomerulus may be responsible for the subsequent development of immune complex-

mediated glomerulonephritis. The occurrence of such a phenomenon could be investigated by extension of immunofluorescent and antibody elution studies to include the detection of virus specific antigens and antibody.

Lymphocytic choriomeningitis virus in mice and Aleutian disease in mink are animal models which indicate another possible role for viruses in the genesis of renal disease. Persistence of virus infection may result in the development of viral antigen-antibody complexes which passively filter out in the kidney and cause glomerulonephritis. Although no analogous situation with persistent viremia and tolerant virus infection has as yet been identified in man, persistence of virus can occur following acute virus infection. The isolation of measles virus from brain tissue of a patient with subacute sclerosing panencephalitis one year following immunization with live measles vaccine accentuates the potential role of persistent viruses in human disease and emphasizes the need for caution in the use of live virus vaccines. The finding of virus-like filaments and particles in renal glomeruli and the demonstration of significant serologic titers implicating a virus infection, particularly in patients with SLE, further suggests an association of persistent virus with some forms of renal disease.

As yet, there is no direct evidence that any form of human renal disease is caused by a virus. However, even circumstantial evidence should suffice to emphasize the urgent need for extensive virologic investigations of chronic renal disease. There are over 10,000 cases of chronic glomerulonephritis a year which require dialysis or transplantation for survival. The hope for the future is that this common disorder can be limited by identification and elimination of such a causative agent as a virus.

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Furosemide and Ethacrynic Acid in Renal Insufficiency

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The advent of the powerful diuretics ethacrynic acid and furosemide has made it easier to increase the excretion of sodium and water in edematous patients who suffer impairment of renal function or other causes of resistance to diuretics. Because of the high potency and efficacy of these drugs, careless use may be disastrous. Nevertheless, this increased ability has not carried with it an unreasonable risk of toxic side effects.

In addition to their natriuretic and diuretic effects in such difficult to manage patients, both furosemide and ethacrynic acid have been used extensively in the prophylaxis and management of acute renal failure, as well as in some patients with terminal renal failure. Much has been written on the sites of action and pharmacology of these drugs, and several reviews are available.^{7, 25, 41} The precise mechanism of action of these drugs is unknown, but clearly the dose response curves of both ethacrynic acid and furosemide are much steeper than those of other diuretics. The reasons for this are not known. Possibly these drugs achieve higher concentrations at the specific site(s) of action. They may produce greater inhibition of a particular site, or they may inhibit multiple sites.

The *cellular* mechanisms by which these diuretics produce their effect on water and electrolyte excretion are not clearly understood. In theory, they might (1) inhibit the metabolic processes that energize sodium transport (by direct effects or by causing anoxia); (2) inhibit active transport by a variety of effects on the basal or luminal cell membranes; (3) reduce the permeability of the luminal membrane; (4) increase the permeability of the basal membrane so that sodium and water leak back into the cell; (5) cause a redistribution of blood flow within the kidney, changing the predominant pattern of nephron perfusion.

Convincing evidence for any of these hypotheses is lacking. A self-evident fact, often given short shrift, is that demonstration of a meta-

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bolic effect ~~does~~ not necessarily indicate the mechanism of action of a diuretic. Both ethacrynic acid and furosemide are known to inhibit glycolysis in vitro,^{22, 27} perhaps analogously to a classical inhibitor of glycolysis, iodoacetate, which can also cause a significant natriuresis.^{51, 57} However, it would be unwise to conclude that this is a cause and effect relationship. Furosemide, when given intravenously, is followed by *increased* concentrations of lactate in renal cortex and medulla,⁶ despite the inhibitory effects on glycolysis demonstrated in vitro. It is possible that the differing in vitro and in vivo effects of furosemide on metabolism are dependent on local diuretic concentration. Concentrations achieved in rabbit renal cortex and medulla 30 minutes after the injection of 20 mg. per kg. furosemide resulted in concentrations of 91 and 579 micrograms per gm. of tissue protein respectively.²⁸ This is somewhat lower than the concentrations inhibitory of glycolysis in vitro. However, even this explanation of the difference in effects is not satisfactory, since the metabolic effects might depend on concentration in tubular cells or organelles following active transport. Of possible relevance to the specific renal effect of furosemide is the fact that liver slices incubated in the same concentration of furosemide (0.76 millimole) as kidney cortical slices show *stimulation* of aerobic glycolysis, while kidney slices show inhibition.²⁸

A possible explanation given by Cannon⁶ for the increased rate of glycolysis after administration of ethacrynic acid and furosemide is that the drugs inhibit oxidative pathways. However, in studies in which fatty acids are used as substrate for cortical slices, there is no such inhibition.²⁸ Further, oxygen consumption of kidney slices in vitro is increased following furosemide injection in vivo.⁶⁰ The crux of the problem is that the relationships of the metabolic effect to active transport in the intact organ have never been satisfactorily established.

After intravenous injection of either drug (5 mg. per kg.) in dogs, a marked natriuresis accompanied by an increase in blood flow was observed. However, no change in oxygen consumption was found, leading the authors to suggest that these diuretics do not inhibit active sodium transport, but rather influence cell membrane permeability. In an earlier examination of this, Ulrich⁵³ studied the effect of furosemide in microperfused rat proximal tubules. He found that the drug reduced active sodium transport but did *not* alter the permeability of the cells to radioactive-labeled sodium and chloride. A further possibility to account for the lack of effect on oxygen consumption is that furosemide and ethacrynic acid largely affect glycolytic metabolism (as discussed above). Another example of the lack of correlation between a metabolic and diuretic effect is the discrepancy between inhibition of Na-K-ATPase (sodium-potassium-dependent adenosine triphosphatase, a membrane enzyme intimately involved with cation transport) in rat kidney by both furosemide and ethacrynic acid and the relative lack of diuretic effect by the latter. Furosemide is diuretic in this species. The inhibition of Na-K-ATPase by para-chloromercuribenzoate, a nondiuretic mercurial, also points out the difficulties in ascribing diuresis to this mechanism. Contrarily, Cole et al.¹² showed that an ethacrynic acid analogue does not inhibit Na-K-ATPase, but is a potent diuretic.

Recently the role of renal hemodynamic changes in causing diuresis following use of ethacrynic acid and furosemide has been examined. Birtch et al.,⁵ using external counting of krypton-85 found that outer medullary and juxtamedullary blood flow were reduced following intrarenal arterial injection of either diuretic. Cortical blood flow was increased. Initial reduction of total renal blood flow coincided with the onset of diuresis. This was followed by an increase, but diuresis continued even after total renal blood flow had returned to its control value. These authors suggest that the redistribution of blood flow is an important component of the action of the drugs. However, they cannot say whether the decrease is secondary to depression of metabolism in localized areas. Not answered by this study is the question whether natriuretic doses given orally or systemically are similarly accompanied by redistribution in blood flow.

Dluhly et al.¹³ examined the vasoactive properties of ethacrynic acid in the in vivo perfused dog kidney under conditions of either constant flow or constant pressure. They also found an initial decrease in renal blood flow followed by an increase whether or not ethacrynic acid was given into the renal artery or systemically. Systemic blood pressure did not decrease. An increase in renal blood flow was associated with augmentation of the natriuretic response, but was not necessary for the natriuresis to occur. Vasodilatation and natriuresis could not be separated in time. Body fluid depletion was associated with a rise in renal vascular resistance despite continuing natriuresis. Fluid repletion was associated with an increase of natriuresis and a fall in renal resistance. The therapeutic approach to the management of acute or chronic renal failure whereby large doses of the diuretic are used after full fluid repletion has theoretical support in this finding. Natriuresis is not necessarily correlated with vasodilatation in this perfused kidney preparation, since both the diuretics meralluride and chlorothiazide increase renal vascular resistance, whereas the antinatriuretic antihypotensive drug diazoxide decreases resistance.

Renal clearance measurements in the human subject and in the dog, and micropuncture studies in a variety of experimental animals, have placed the site of action of both ethacrynic acid and furosemide in the ascending limb of the loop of Henle, and the distal convoluted tubule. In addition, an effect of furosemide in the extracellular volume-expanded dog has been shown in the proximal convoluted tubule. In analyzing the specific effects of large doses of furosemide and ethacrynic acid, it is not at all clear if it is the vasoactive effects which account for the marked inhibition of sodium reabsorption that is seen in experimental studies or in the adequately treated patient with renal insufficiency. Despite the clinical use of ethacrynic acid and furosemide combined with mannitol to effect a change in renal hemodynamics, Ludens et al.²⁹ found that furosemide increased renal blood flow only in saline loaded dogs, but not in those loaded with mannitol. They suggested that the change in vascular resistance depended on the *initial* intrarenal resistance. Because total renal resistance after both mannitol and saline loading was the same, there would have to be differences in *segmental resistance* for this theory to be tenable.

The mannitol-loaded animal would thus have decreased segmental resistance, whereas the saline-loaded animal would not. Alternatively, mannitol might prevent (or interfere with) the local effect of the diuretic. The reason for the apparent clinical success of these diuretics with mannitol might lie in the comparatively huge doses used in the clinical situation. In the experimental study quoted, the highest dose of furosemide used was 1 mg. per kg. The small dose may also explain the lack of effect on the inulin clearance noted in this study, in contradistinction to the small but definite increases noted in some clinical studies. In view of the marked vasoactive effects of both ethacrynic acid and furosemide, the study of Ludens et al.³⁰ on the differential effects of furosemide on the renal and limb blood flow is illuminating. They found that furosemide increased renal blood flow, but the limb flow (even after injection into a limb artery) was markedly decreased. When furosemide was given to a bilaterally nephrectomized animal, no decrease in limb blood flow was seen, suggesting that a vasoconstrictor of renal origin was required. That the secretion was due to volume depletion is unlikely, since Vander and Carlson³⁴ showed that increased renin secretion occurred after furosemide administration even when the experimental animal was in fluid balance. However, the degree of total body fluid volume depletion, in the experiments of Ludens et al., may have influenced the limb blood flow.

Clinical significance of possible reduction in blood flow in terms of the effects on coronary, cerebral, and other vascular beds has not been established.

Hollenberg et al.²¹ have shown that an invariable finding in their patients with oliguric renal failure was redistribution of intrarenal blood flow. This was shown by the external krypton-85 technique to be confirmed in some patients' radiographic findings. The most obvious finding was a reduction in cortical blood flow. That furosemide and ethacrynic acid have been shown to have an opposite effect to this by increasing cortical blood flow at the expense of outer medullary or juxtaglomerular flow is of probable therapeutic significance.

CHRONIC RENAL FAILURE

It is a well appreciated clinical fact that the response to thiazides, mercurials, spironolactone, and triamterene by patients with marked impairment of renal function is often meager. Consequently, successful use of furosemide and ethacrynic acid has led to a real advance in therapeutics. Wide experience is portrayed in the pertinent literature, and the methodology and potential dangers of high dosage diuretic therapy have been satisfactorily defined. Nevertheless, it is felt that the full scope of this type of therapy has yet to be evaluated.

Reubi¹¹ related diuretic responsiveness to impairment of glomerular filtration rate. He suggested that diuretics increase by a specific multiplying factor the percentage of filtered sodium rejected under control conditions (i.e. before the administration of the diuretic), provided that

the total rejection remains below a certain limit. Both furosemide and ethacrynic acid are effective even when 30 to 40 per cent of the filtered sodium is rejected (corresponding to a glomerular filtration rate of 3 to 10 ml. per min.), provided that the dose used is sufficiently high. In agreement with this are the findings of Heidland and Hennemann,¹⁹ that the rate of diuresis after furosemide is relatively higher with lower filtration rates. They found that catecholamine excretion increased following small doses of both furosemide and ethacrynic acid, and that the rate of excretion was directly related to glomerular filtration rate. They suggested that the relatively low increase in fractional fluid elimination in patients with normal kidney function might be due to humoral effects which cause changes in renal blood flow or increased formation of cyclic 3',5'-AMP or both. In patients with impaired renal function, these humoral effects might be reduced.

In discussing the selection of a specific diuretic for use in patients with chronic renal failure, Kleeman²³ suggested that pertinent factors include the etiology of the renal failure (in particular whether the cause was "glomerular" or "tubular"), the state of renal function, the effective dose, the electrolyte composition of the urine after diuretic administration, the extent of water loss, and the presence and quantitation of diuretic toxicity. A survey of the major publications on the use of ethacrynic acid and furosemide suggests that many of these factors have been satisfactorily evaluated. It seems clear that to the appropriate dosages, patients with all types of renal failure — irrespective of etiology — have a diuretic response. Similarly, even in terminal renal failure, high dosage therapy has been effective.

Berman and Ebrahimi¹ found that patients with severe renal failure did not respond to ethacrynic acid or furosemide, but the total daily doses used in their study were between 80 and 150 mg. which in retrospect may have been too low. Maher and Schreiner³² used ethacrynic acid in doses of 2 to 4 mg. per kg. every 6 hours and noted an excellent response in 5 patients with creatinine clearances of less than 7 ml. per minute. Two uremic patients who were given up to 4.8 gm. per 26 hours developed hypoglycemia. This seems to be the only report of this particular metabolic effect of this drug. McKenzie et al.³¹ used blood urea furosemide in daily doses up to 980 mg. in 15 patients with nitrogen levels greater than 100 gm. per 100 ml. and found a satisfactory response in 12 of these.

Edwards et al.,¹⁴ in a comprehensive analysis using a method of randomized treatments, found that ethacrynic acid and furosemide were equally potent diuretics. Nineteen of 22 patients with an average glomerular filtration rate of 20 ml. per minute responded to a mean dose of ethacrynic acid of 150 mg. with a loss of 3.8 mg. per kg. No particular relationship between the etiology of renal disease and the response to therapy was noted. No significant effects of the drugs on urine sediment were observed. Seven patients of the 22 developed a hypochloremic alkalosis.

Muth³⁸ reported a careful study of the effects of high dosage furosemide in a group of patients with significant renal insufficiency that was

refractory to the standard diuretic agents. In addition to demonstrating that the drug was effective over a wide range of abnormal serum electrolyte concentrations, he showed that a clinically useful diuretic response was produced with creatinine clearances down to 2 ml. per minute, although most patients studied had clearances over 10 ml. per minute. The 24 hour dosage range for maximum diuresis was between 80 and 1400 mg. for oral administration and between 80 and 4000 mg. for intravenous use. Therapy was continued at high dosage levels for up to 2 years. Responses in patients with diabetic glomerulosclerosis, chronic glomerulonephritis, chronic pyelonephritis, and hypertensive renal disease were comparable. In an earlier study, Muth³⁷ had found that ethacrynic acid was not well tolerated, owing to gastrointestinal side effects. Laragh²⁵ discussed the principles of high dosage diuretic administration. He suggested that, when possible, therapy should be intermittent, with cautious stepwise increases in dosage accompanied by careful observation of weight, urine output, electrolyte excretion, serum electrolyte concentration, and renal function.

Silverberg and Kjellstrand⁴⁷ used high doses of furosemide in the treatment of resistant nephrotic edema. In 3 patients, an oral dose of 600 mg. resulted in satisfactory diuresis. Of interest was the demonstration in one patient that a dose of 1200 mg. was not effective until a thiazide was added to the regimen. Similarly, Ledingham²⁶ found that thiazides could augment the effect of ethacrynic acid. However, it is generally agreed that with high doses of ethacrynic acid and furosemide, the addition of thiazides contributes little or nothing to diuretic management of patients with renal insufficiency. Gregory et al.¹⁷ studied the short term effect of furosemide on electrolyte and water excretion in patients with severe renal disease. In 11 adults with a glomerular filtration rate of 1 to 3 ml. per minute, doses of 1.5 mg. per kg. were used. The absolute increase in sodium excretion was *inversely related to the magnitude of the glomerular filtration rate*, and there was little clinical benefit in patients with filtration rates less than 5 ml. per minute. This is in contrast to other reports, in which higher doses have been successfully used at this level of renal function.

White et al.⁵⁶ investigated the effectiveness of 100 mg. of furosemide administered intravenously in 9 patients with glomerular filtration rates of 4 to 14 ml. per minute. Sodium clearance increased from a range of 4 to 8 per cent of creatinine clearance to a range of 7 to 35 per cent, a relative increase similar to that found in normal subjects after an equal dose. In 4 patients with a glomerular filtration rate of 1 to 4 ml. per minute, continued 100 to 200 mg. doses of furosemide every 4 hours resulted in weight losses of 5 to 11 kg. On the basis of balance studies, White et al. suggested that part of the loss must have been due to gastrointestinal sodium loss. This has not been confirmed by others.

Reubi¹¹ found that the ratio of inulin clearance during control periods to inulin clearance during furosemide administration was greater than one in 16 of 21 patients. Increase in the *ratio* was directly related to a *decrease* in control glomerular filtration rates. Vorburger et al.,⁵⁵ Schirmeister et al.,⁴² and Barcelo et al.³ have found transient

increases in the glomerular filtration rates after intravenous injection. Other authors^{4, 50} have not confirmed this, but the variables of dose and degree of functional impairment complicate interpretation. Of particular interest is the study of Heidland et al.,²⁰ in which 100 mg. doses of furosemide were followed by 1000 mg. doses in patients with glomerular filtration rates (inulin clearances) less than 5 ml. per minute. While the 100 mg. dose increased inulin clearances from 3.1 to 3.9 ml. per minute, the 1000 mg. dose increased it from 3.6 to 5.2 ml. per minute. Differences of this degree, although small in absolute terms, could be of real benefit in the management of patients with terminal renal failure, particularly those in whom dialysis can be postponed or delayed.

In the same study CNa/GFR increased 172 per cent after the higher dose, compared to an increase of 35 per cent after the 100 mg. dose. It is common practice now to utilize both high salt intake and high doses of furosemide in certain patients with chronic renal insufficiency. For example, Clyne et al.,⁹ in their discussion of the approach to therapy of patients with renal disease (with emphasis on the use of dipyridamole and anticoagulants), mention the success of the use of furosemide (up to 1 gram per day) combined with high salt intake in improving function in patients referred for hemodialysis or renal transplantation. Spilkin and Weller⁴⁹ gave doses of 200 to 800 mg. of furosemide per 24 hours to patients with a creatinine clearance of less than 3.5 ml. per minute who were undergoing intermittent peritoneal dialysis. In 8 patients, use of this dosage regimen (as the only variable) prolonged the interval between peritoneal dialysis from 18 days to 23 days during control periods.

Review of other papers in which the use of large doses of these drugs has been described in the management of renal failure show a definite trend. Increasingly large doses are being used, particularly of furosemide, and there appears to be no obvious upper limit in the literature. It is important to emphasize that the respective package inserts do not recommend doses of oral furosemide greater than 600 mg., and of ethacrynic acid, greater than 400 mg. A suggested upper limit for intravenous therapy is not given by the manufacturers of furosemide. When large doses are being used, the patient should be in the hospital. Therapy should be initiated with relatively low doses, for example, 80 mg., and then the dosage should be increased rapidly if response is unsatisfactory. Both oral and intravenous therapy are effective, but in a patient in uremia the factor determining response may be the peak level achieved. Under these circumstances intravenous therapy may be preferable.

Knowledge of the blood levels reached after oral or intravenous use and the plasma half time of furosemide is of value. For example, after a 200 mg. dose given to a 60 kg. patient with a creatinine clearance of 3 ml. per minute, a level of 30 micrograms per ml. is reached after 5 minutes, whereas the same dose given orally to the same patient peaks at 8 micrograms per ml. after 2 to 3 hours.²⁸ The half-life of furosemide in plasma of patients in renal failure is such that the drug needs to be given at least daily to achieve adequate therapeutic levels. However, there is some evidence that repeated administration of furosemide results in accumulation of the drug in the kidney.⁴⁶

The effect of the high body fluid concentrations of these drugs on metabolic processes in nonrenal tissues is as yet unknown. It is clear that both ethacrynic acid and furosemide have significant effects on the *in vitro* metabolism of a variety of tissues including red cells, kidney, bladder, heart, and liver, but concentrations at which they effectively inhibit metabolic processes in *in vitro* studies are not approached, except when the large dosages mentioned above in the management of renal insufficiency are utilized.

A study by Seno et al.⁴⁶ is of some help in considering the sites of metabolic effects on these drugs. After a single intravenous dose of ³⁵S-labeled furosemide, levels of the drug were highest in kidney, then in liver, spleen, muscle, and brain.

CASE REPORT. Mr. L. D., aged 43, was found to have hypertension and impaired renal function in 1965, when he presented with subarachnoid hemorrhage and right hemiparesis. In 1968 a percutaneous renal biopsy showed chronic proliferative glomerulonephritis. A trial of azathioprine therapy was unsuccessful, and by the end of 1969 his creatinine clearance was ± 5 ml. per minute, and 24 hour protein excretion was ± 3 gm. Peritoneal dialysis was performed in January 1970, and his renal function equilibrated, with a blood urea nitrogen level of 95 mg. per 100 ml. and serum creatinine of 18 mg. per 100 ml. Renal function gradually deteriorated over the next 3 months. Creatinine clearance on an 80 mEq. sodium intake was 1.5 ml. per minute.

Urine output averaged 700 ml. per day. Sodium output was 50 to 70 mEq. per 24 hours. Dialysis was required every 8 days. He was treated during this time with furosemide, 200 mg. daily, orally. The daily rate of rise of serum creatinine was 0.8 mg. per 100 ml. On increasing furosemide dosage to 400 mg. daily, and with continued salt loading, urine output increased to 1000 to 1200 ml. per 24 hours, and creatinine clearance increased to 3 ml. per min. Sodium excretion was now 90 to 100 mEq. per 24 hours. The period of time between dialyses increased to 18 days, and the patient remained well clinically. The daily rate of rise of serum creatinine during this latter period was 0.3 mg. per 100 ml.

ACUTE RENAL FAILURE

A therapeutic regimen in use is as follows: After the initial assessment of the patient, an attempt is made to induce diuresis. If the patient is *not* overhydrated or does not have a marked increase in jugular venous pressure as judged clinically or by measurement of the central venous pressure, 1000 ml. of 0.9 per cent saline (or isotonic mixtures of saline and bicarbonate if the patient is markedly acidotic) are given over 60 to 90 minutes. This is combined with the injection of mannitol (25 gm.) intravenously, and furosemide or ethacrynic acid (200 mg.) intravenously. The response to these agents is observed by following hourly urine volumes, by the temporary insertion of a urethral catheter if necessary. If the patient is already well hydrated, the diuretic may be used without the administration of mannitol or saline.

Both furosemide and ethacrynic acid have been extensively used in the prophylaxis and early management of patients with acute renal failure. It seems reasonably clear that a small proportion of patients in whom acute oliguric renal failure is unresponsive to rehydration and mannitol infusion may diurese after intravenous ethacrynic acid or furosemide.

Cantarovich⁸ studied the effectiveness of different dosages of furosemide in 36 patients with acute renal failure. A control group receiving no drug, one group receiving 600 mg. daily, and one receiving from 100 to 3200 mg. by doubling the daily dose, were defined. The duration of anuria was 19, 12, and 6 days in the three groups, respectively, and the level of 2000 ml. diuresis was reached in 23, 14, and 9 days, respectively.

Maher and Schreiner,³² Auger et al.,² Chinitz et al.,¹¹ and Kjellstrand²⁴ reported the successful use of ethacrynic acid (50 to 100 mg. intravenously) in mannitol-resistant acute oliguric renal failure.

Gilmore and Mann¹⁶ found that 8 of 12 patients in acute renal failure who were not given mannitol responded with a diuresis after receiving 50 mg. of ethacrynic acid. Merrill²⁵ recommended the routine use of ethacrynic acid or furosemide in patients with acute oliguric renal failure.³⁵

An interesting use of these diuretics has been in the management of patients with acute oliguria of unknown cause occurring in the early postoperative period after renal transplantation. Anderson et al.¹ found that 4 of 5 patients given ethacrynic acid (50 mg.) and mannitol (25 gm.) responded with an immediate diuresis. One patient who had a poor response was later found to have had acute graft rejection.

SOME PROBLEMS ASSOCIATED WITH HIGH DOSAGE DIURETIC THERAPY

Because of the diuretic resistance associated with severe renal failure, severe electrolyte and water depletion is rarely a problem after therapeutic doses of ethacrynic acid and furosemide. However, when a large dose of furosemide or ethacrynic acid is given to a patient in the clinical situation of oliguria due to questionable acute renal failure, a marked and potentially hazardous diuretic response may occasionally be observed. A similar situation may occur when treating oliguria developing subsequent to renal cadaveric transplantation. Gradual depletion of sodium chloride, potassium, and dehydration can occur even in the patient with oliguria and terminal renal failure. The acute effects on water, electrolytes, and acid base-balance are well known and do not require further discussion here.

Both ethacrynic acid and furosemide can aggravate the hyperuricemia present in the majority of patients with chronic renal failure. This can usually be satisfactorily controlled by small doses of allopurinol.

The impaired glucose tolerance typically found in patients with chronic renal insufficiency can be further worsened by furosemide, but this is rarely a clinical problem in the circumstances considered here.

There is no practical difference in the potency of ethacrynic acid and furosemide. Both drugs have been successfully used in high doses in the management of acute and chronic renal insufficiency, with no apparent differences in therapeutic effect. There seems to be a greater incidence of gastrointestinal symptoms with ethacrynic acid than with furosemide, and Slone et al.^{4b} suggest that the frequency of gastro-

intestinal bleeding is significantly higher after intravenous ethacrynic acid therapy than after treatment with oral furosemide. No similar report concerning intravenous furosemide has appeared.

The major side-effects unrelated to the diuretic or metabolic effects that have been commonly reported following the use of high dosages of these diuretics in renal failure have been loss of hearing, tinnitus, and vertigo. Major attention has been given to ethacrynic acid. Maher and Schreiner³² reported acute transient deafness after intravenous injection, and vertigo after oral administration. Schneider and Becker⁶³ found that transient deafness developed within 12 hours of the first dose in 5 patients with renal impairment, and suggested that the deafness was related to retention of an ethacrynic acid metabolite. Pillay et al.⁴⁰ described 5 uremic patients with deafness. In 1 patient deafness was permanent. Two others who died shortly after treatment did not regain normal hearing. One patient complained of deafness 90 minutes after 200 mg. ethacrynic acid had been given intravenously.

Hanzelik and Peppercorn¹⁸ described a patient in chronic renal failure who complained of hearing difficulty 10 minutes after administration of 100 mg. ethacrynic acid. They raised the possibility of direct toxicity to the auditory nerves. Similarly, Ng et al.³⁹ reported virtually instantaneous deafness after ethacrynic acid administration in a uremic quadriplegic patient.

Mathod and Klein³³ suggest that there is a synergistic effect of ethacrynic acid and small doses of aminoglycoside antibiotics in producing auditory loss. Matz et al.³⁴ found severe destruction and absence of outer hair cells but presence of normal inner hair cells in a patient who had died in hepatic coma. The patient received ethacrynic acid (50 mg.) and had complained of hearing loss 20 minutes later. She had also received 18 gm. of neomycin orally during the 7 days prior to diuretic therapy.

Schwartz et al.⁴¹ suggested that ethacrynic acid or its congeners may form toxic complexes with organic compounds retained in azotemic patients. Another approach to the problem was made by Wilson and Juhn, who found that the potassium concentration of the perilymph of guinea pigs given large doses of ethacrynic acid (50 mg. per kg. per 48 hours) was higher than that of controls. They suggested that the ototoxic property of ethacrynic acid may be related to the inhibition of a sodium-potassium transport system. However, the dosage used was even higher than that employed clinically.

In a recent report on the ototoxic effects of furosemide, Schwartz et al.⁴⁵ described 5 patients who had impaired hearing ability, vertigo, and tinnitus for up to 5 hours after intravenous administration. However, the doses used were a good deal higher than those doses of ethacrynic acid that have been associated with deafness. Heidland and Wigand²⁴ found that infusion of 1000 mg. of furosemide (25 mg. per min.) induced reversible loss of hearing, affecting mainly the medium and high acoustic frequencies. A dose of 600 mg. administered at a rate of 15 mg. per minute induced very slight reversible impairment of hearing in 5 of 10 patients. However, when similar doses were given at a rate of less

than 5.6 mg. per minute, no ototoxic effects were noted. The authors concluded that the effect was a function of dose-time quotients, and that high doses should be given only over a prolonged period. For example, 1000 mg. furosemide should be given intravenously in not less than 4 hours.

To place these reports of ototoxicity in perspective, it is interesting to note that Merrill, in a recent review of the management of acute renal failure, suggested the routine use of a test dose of 200 mg. of ethacrynic acid administered intravenously.³⁵ He did not mention possible hearing hazards. When challenged on this point, Merrill¹⁰ stated that in 3 years of use of this regimen in his unit, he had encountered only 3 cases of transient deafness and none of permanent deafness. However, he expressed no objection to the use of furosemide for the same purpose. The available literature and general clinical experience would suggest that furosemide is the safer drug from this point of view.

CONCLUSION

The cautious use of high doses of furosemide and ethacrynic acid has simplified the management of a proportion of patients in acute or chronic renal failure. Such high doses should be used only when there is careful clinical and laboratory control, and with awareness of the possible adverse effects of this therapeutic approach. Controlled trials are still required to evaluate the possible clinical benefits of these potent diuretic drugs in established renal failure, but the available evidence would suggest that they have a role in a variety of clinical situations.

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The Conservative Management of Acute Oliguric Renal Failure

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As more definitive and extensive forms of treatment for renal failure such as chronic hemodialysis and renal transplantation become more generally accepted, the distinction between acute and chronic renal failure has become less important. Many patients who present with the classic syndrome of acute renal failure do not recover sufficient renal function to maintain life without artificial means; on the other hand, some patients present with exacerbation of chronic renal disease which may in part be reversible. Further, the diagnosis and prognosis is often unknown prior to thorough investigation and evaluation. Nevertheless, acute renal failure can be defined as an acute reduction in renal excretory function which occurs in a clinical setting known to precipitate the condition.

CLINICAL COURSE OF ACUTE RENAL FAILURE

The Precipitating Event

The syndrome of acute renal failure may follow trauma, septicemia, severe dehydration, allergic reactions, or nephrolithiasis; or it may accompany systemic autoimmune diseases or follow ingestion of a nephrotoxic agent. Regardless of the primary etiology, the final common pathway in most instances is hypotension, with a decrease in renal blood flow and alteration in renal hemodynamics.

If an attempt is to be made to prevent irreversible renal failure, the physician must be cognizant of those clinical conditions in which acute renal failure may occur.

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The Period of Oliguria or Anuria

Clinically, this is manifest by oliguria (arbitrarily defined as a urine volume of less than 300 ml. per 24 hr.) or anuria. The period of oliguria or anuria is accompanied by a gradual to rapid rise in serum concentrations of substances normally excreted by the kidney, and progressive deterioration of normal chemical homeostasis.³³

Occasionally a patient is seen with so-called "high-output" renal failure, in which there is a rapid rise in serum concentration of urea, creatinine, and other components, despite an adequate urine output. This probably represents a condition corresponding to the early diuretic phase of acute oliguric renal failure.

The oliguric period is accompanied by a rise in serum concentrations of end-products of protein metabolism and cellular breakdown products. In general, carbohydrate and fat are metabolized completely to carbon dioxide and water; and the kidney is responsible only for the excretion of excess water. The end-products of protein metabolism, on the other hand, rely primarily on the kidney for their excretion. These substances include: urea (the major end-product of protein metabolism); creatinine (muscle protein metabolism); uric acid (nucleoprotein metabolism); organic acids, particularly phosphate and sulphate; and the intracellular cations, potassium and magnesium. In addition, there are many other circulating intermediaries in protein metabolism, including indoles, phenoles, indicans, peptides, polypeptides, amino acids, and guanides.

The period of oliguria or anuria persists from 7 to 21 days, although it may be very brief (sometimes persisting only for hours, particularly preceding the "high-output" type of acute renal failure). In occasional patients it may persist for as long as 60 to 70 days, with subsequent recovery of some degree of renal function.

The Diuretic Phase

With luck, the anuric or oliguric phase is followed by the diuretic phase, heralded by a gradually increasing urine output which may at times reach 4 to 6 liters per day. Rarely does the urine volume exceed this, and this probably occurs only when the patient has been significantly overhydrated during the oliguric period. It is not uncommon for the patient's clinical condition and biochemical studies to deteriorate for several days despite diuresis. The blood urea nitrogen and serum creatinine levels will often rise for 3 to 5 days after the onset of diuresis before leveling off, then decreasing. Undoubtedly, this is due to a very low glomerular filtration rate initially. Obviously, the diuretic phase is associated with considerable loss of water and electrolytes and presents as distinct a challenge to the physician as does treatment during the oliguric period.

During the 2 to 4 week period encompassing the oliguric and diuretic phases of acute renal failure, conservative treatment is the fundamental principle in management. This can be supplemented by peritoneal dialysis or hemodialysis, but can never be replaced by these forms of treatment.⁹

Period of Convalescence

There is an extended period of convalescence which should be appreciated by the physician. Many patients are debilitated and in a poor nutritional state owing to the primary disease which precipitated acute renal failure. In addition, management of acute renal failure is extremely taxing, and it may be many months before full physical rehabilitation can be accomplished. Complete restoration of renal function may not occur for as long as 6 to 12 months. As expected, the most sensitive parameter of renal function—the ability to concentrate the urine—is the last to return to normal.

There are conflicting reports on renal functional status after prolonged follow-up of patients who have recovered from acute renal failure. The most encouraging is by Shriner et al.³¹ who demonstrated on follow-up renal biopsies in a number of patients that renal histology was completely normal. Other reports suggest that, in general, the ultimate prognosis for complete restoration of normal renal function depends primarily on the severity of the original insult and also on the duration of the period of oliguria or anuria.²⁷

MANAGEMENT OF THE PATIENT WITH ACUTE RENAL FAILURE

Initial Assessment

When a patient presents with oliguria or anuria, a treatable cause is sought for, and an anatomic and histologic diagnosis is desirable. After an initial assessment to rule out urinary tract obstruction,¹ an attempt to induce diuresis and improve renal blood flow can be instituted as follows: 1000 ml. of normal saline intravenously in 60 to 90 minutes; mannitol, 25 gm. intravenously; and ethacrynic acid, 200 mg., or furosemide, 160 mg., intravenously.

This combination causes an increase in renal plasma flow,⁷ a decrease in intrarenal vascular resistance,³ and a redistribution of intrarenal blood flow to the area of ischemia, i.e., the renal cortex.²¹ If a diuresis is established within 3 hours (60 to 100 ml. per hr.), this should be sustained by replacing the measured hourly urine volume with half normal saline. If urine flow drops below 30 ml. per hr., the same dose of mannitol or ethacrynic acid may be repeated every 6 to 8 hours.

Once diuresis is established, a good urine flow should be maintained for 24 to 36 hours. After this period, the danger of irreversible renal failure has passed. If, however, a diuresis does not ensue, the patient must be treated as being in acute oliguric renal failure.

The regimen described must obviously be compromised in the presence of cardiac decompensation—the plasma-expanding administration of saline must be eliminated.

Necessary diagnostic procedures must be undertaken to assure that the acute renal failure is not produced by a readily reversible cause such as obstructive uropathy. Further, acute renal failure secondary to

collagen-vascular diseases, particularly systemic lupus erythematosus, may be responsive to corticosteroid or immunosuppressive therapy. Acute renal failure secondary to a consumptive coagulopathy, hemolytic uremic syndrome or thrombotic thrombocytopenic purpura, should be treated with anticoagulants.

Oliguria secondary to hypercalcemia, myeloma kidney, or acute uric acid nephropathy may be readily reversible. Since the prognosis of patients presenting with acute renal failure is so poor, every effort should be made to search for a reversible cause.

Some of the diagnostic procedures employed may be quite taxing to the debilitated patient, and therefore the clinical condition should be stabilized before thorough diagnostic evaluation is undertaken. In some instances, peritoneal dialysis or hemodialysis is required prior to investigation to stabilize the patient's clinical condition.

BIOCHEMICAL STUDIES. The blood urea nitrogen, serum creatinine, electrolytes, calcium, phosphorus, uric acid, and glucose should be determined immediately and followed closely. The blood urea concentration may not be a good index of renal function, because absolute values are a product of a number of factors, and not due to renal excretion alone.¹² The blood urea concentration is also affected by protein ingestion, gastrointestinal bleeding, and rate of tissue catabolism; therefore the most reliable measure of renal function is the level of serum creatinine.

If the clinical picture suggests the presence of a glomerulonephritis or systemic vasculitis, antinuclear antibodies, lupus erythematosus cell preparations, and serum complement levels should be measured. The urinary sodium concentration may also be helpful in differential diagnosis. The concentration tends to be less than 30 mEq. per liter in the presence of a primary glomerulonephritis or vasculitis and greater than 40 mEq. per liter in acute tubular necrosis.²⁰

RADIOGRAPHIC STUDIES. A plain film of the abdomen may disclose a radiopaque stone, thus eliminating the immediate need for an intravenous pyelogram. It can also be used to measure kidney and bladder size.

Infusion pyelography is used to evaluate kidney size and morphology, and may be helpful in demonstrating the patency and configuration of the lower tract. If the blood urea nitrogen is greater than 80 mg. per 100 ml., high-dosage contrast media with delayed films must be used. If the kidneys are not visualized within 6 hours, an examination at 24 hours with tomography—if necessary—is usually adequate.

Cystoscopy and retrograde pyelography are employed if the foregoing procedures cannot rule out obstruction.

The arterial blood supply and possible masses in the kidneys can be evaluated by an arteriogram, a radioisotope renogram, or a renal scan. The patency of the venous system of the kidney can be documented with a venogram or venocavogram.

The voiding cystourethrogram is reserved for those cases in which a malfunctioning bladder or a vesicoureteral reflux is suggested as the etiologic factor for renal failure.

Renal biopsy in patients with acute renal failure should be used to solve major questions of etiology, treatment, and prognosis, provided that

no contraindication exists. The presence of a solitary kidney, bilaterally small kidneys, a significant bleeding diathesis, or an uncooperative patient are absolute contraindications to a percutaneous biopsy.²⁵ A surgical biopsy may carry less morbidity for these patients.

GENERAL CARE OF THE PATIENT WITH OLIGURIC RENAL FAILURE

Fluid Balance

Overhydration was one of the major causes of mortality prior to the introduction of precise fluid restriction as an important therapeutic measure. Careful and accurate records of fluid intake and output plus daily weighings should be observed. As a general rule, it is preferable to maintain the patient in a slightly dehydrated state. In calculating daily water requirements, the liberation of endogenous water from oxidation of fats and proteins must be considered.²⁴ The average caloric expense in a starving patient will produce 400 ml. of endogenous water. Since 800 ml. is the average insensible loss (0.5 ml. per kg. per hr.), it is necessary to replace only 1 half that value, or 400 ml. per 24 hr. If the patient is febrile, each increment of 1° F. causes an increase of 10 per cent in the insensible loss.⁴² All fluid losses, including those from urine, stomach suction, wound drainage, stool, etc., should be replaced every 24 hours by the oral route if possible. When properly treated, the anuric patient should lose about 1 lb/day.²⁴ Any increase in weight reflects overhydration and should be corrected.

Nutrition

The importance of sound nutritional therapy cannot be overemphasized. Through the use of a few basic principles, serious metabolic derangements, poor wound healing, and poor host resistance may be modified.¹³

The first 48 to 72 hours of oliguria are characterized by rapid tissue catabolism and, hence, the most pronounced elevation of the blood urea and other end-products of protein metabolism. During this period, exogenous protein should be avoided. However, this is not true for total caloric intake.²⁸ While data from normal subjects must not be necessarily applied to diseased states,⁴⁰ 100 gm. of carbohydrate per day would appear to have a maximum protein sparing activity. Studies during a hypercatabolic state showed some decrease in urea formation if 1700 cal. or more were provided each day. Clinically, this may be achieved through use of intravenous 50 per cent glucose fat emulsions.²⁸ These mixtures may be valuable if the patient is hypercatabolic or if nutrition was poor prior to the onset of renal failure.

Anabolic steroids can suppress urea formation by decreasing protein breakdown only if adequate caloric intake is present. The effects last for about 2 weeks, and these agents may be a useful adjunct during the oliguric phase. Agents such as norethandrolone and mandrolone phenpropionate are given daily intramuscularly and have few side effects over a short period.^{8, 16, 17}

After 3 to 4 days of oliguria, the rate of tissue catabolism slows and dietary protein can then be added. The use of 20 to 40 gm. protein of high biological activity, such as that found in eggs, as described by Giordano-Giovanetti,¹⁵ has been shown to be most effective. At this stage, the total caloric intake should also be increased to 2000 to 2500 cal. per day with a supplement of multivitamins. Maintenance on this type of diet usually results in a positive nitrogen balance. If repeated dialyses are required, the protein intake should be increased, because 10 to 20 gm. of amino acids may be lost during 6 hours of hemodialysis, and up to 50 gm. of protein may be lost during 36 hours of peritoneal dialysis.⁴⁰ Folic acid, 5 mg. per day, must also be added if repeated dialyses are used.

The basic diet contains 0.5 gm. of sodium, and restricts potassium and phosphorus intake. Raisins, prunes, dates, coffee, and citrus fruits and juices should be avoided. Also, an antacid containing aluminum hydroxide gel (but not magnesium), given three to four times per day is helpful in decreasing phosphorus absorption.

Sodium Balance

The most common cause of hyponatremia is overhydration with electrolyte-poor solutions in the presence of unrecognized oliguria or anuria, or excess oral fluid intake during anuria. These conditions can be treated by rigid fluid restriction, which leads to a gradual increase in the serum sodium concentration. Occasionally, water intoxication with severe hyponatremia is present and hypertonic saline (5 per cent) must be given under careful scrutiny. Electrolyte imbalance of this magnitude is probably an indication for early dialysis.

Asymptomatic hyponatremia generally does not require correction. However, if hyperkalemia is superimposed on hyponatremia, cardiac arrhythmias develop more rapidly,³⁶ so the serum sodium concentration should be treated at the same time that the hyperkalemia is being corrected.

During the anuric phase, total sodium intake should be limited to 500 mg. per 24 hrs. As the diuretic phase approaches, this figure will be greatly increased. During the diuretic phase, frequent values for serum concentrations and spot urine concentrations of sodium will aid in proper sodium replacement. While sodium lost in perspiration and normal bowel function need not be replaced, diarrhea and gastric suction or frequent emesis may cause an excessive loss of sodium, which should be replaced.³⁶

Potassium Balance

Hyperkalemia is a common complication, particularly in the hypercatabolic patient. Total body potassium is unchanged, but the extracellular concentration increases owing to protein and fat catabolism, breakdown of devitalized tissues, metabolic acidosis, and red cell hemolysis. Dialysis can control hyperkalemia; however, there are simple measures that can be life-saving. The first evidence of hyperkalemia is usually seen on the electrocardiogram (bradycardia, arrhythmia, and peaked T waves, Fig. 1).

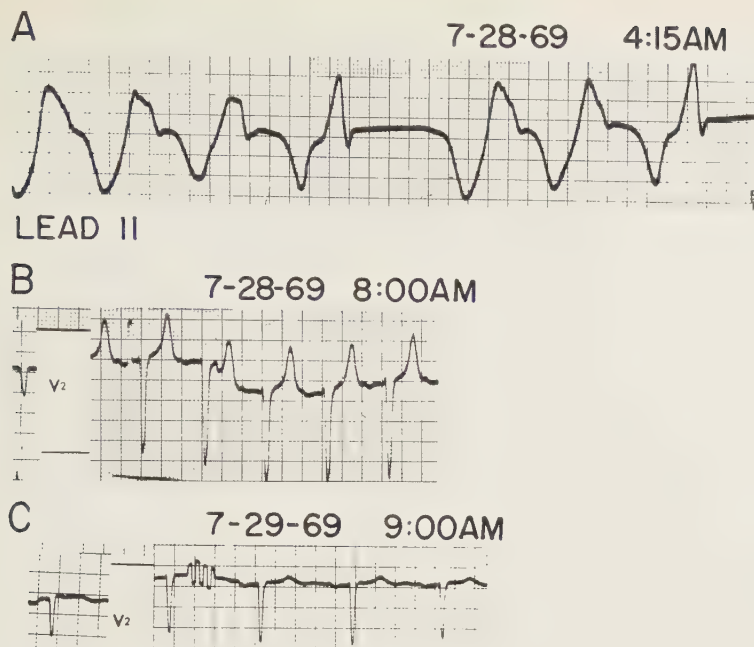


Figure 1. A series of electrocardiograms from a patient with chronic renal failure. A, Serum potassium 8.6 mEq. per liter. Sinus arrest, peaked T waves, and an idioventricular rhythm are noted. B, Serum potassium 7.2 mEq. per liter. Sinus rhythm with a first degree atrioventricular block and peaked T waves are shown. C, Serum potassium 4.3 mEq. per liter. Note the sinus rhythm, and return of T waves to basic pattern.

The main goal in treating hyperkalemia is not to extract potassium, but, more important, to cause an acute intracellular shift of potassium ion. An ion exchange resin polystyrene sulfonate (Kayexalate) is quite effective.^{14, 15} The most rapid method of lowering the serum potassium concentration is to use the resin as a retention enema, since the colon is the major site for potassium exchange. The standard dosage is a mixture of 20 to 60 gm. of the resin with 100 to 150 ml. of sorbitol; the enema should be retained for 30 to 40 minutes. If potassium elevation is anticipated, 15 gm. of resin in 30 ml. of sorbitol can be given orally three times per day. The sorbitol may also cause an osmotic diarrhea and enhance potassium loss. Since polystyrene sulfonate exchanges sodium for potassium, it can act as a dangerous sodium donor^{5, 6} with repeated usage, contributing 3 mEq. of sodium for each gram of resin.

The presence of devitalized tissue can cause a rapid increase in the extracellular potassium concentration in acute renal failure; extensive debridement of a devitalized limb or other organs can be life saving.

Calcium Metabolism

In general, the serum calcium concentration is decreased in acute renal failure, but does not require therapy. If hypocalcemia is present with a severe metabolic acidosis, intravenous calcium should be given before the acidosis is corrected—otherwise cardiac arrest or tetany can

result.³⁶ Also, if multiple transfusions of citrated blood are given, 1 gm. of calcium gluconate or chloride should be given intravenously for each four units of blood. Transfused blood can also contain a large amount of potassium, depending on the period of time before usage.

MEDICAL EMERGENCIES AND COMPLICATIONS OR ACUTE RENAL FAILURE

Hyperkalemia

The emergency therapy for hyperkalemia is outlined in Table 1. Intravenous sodium bicarbonate (40 to 80 mEq.) acts rapidly by correcting the acidosis, causing an intracellular shift of potassium ion. This effect lasts about 2 hours. This can be followed by 250 ml. of 25 per cent dextrose or 100 ml. of 50 per cent dextrose and 20 units of regular insulin intravenously.²⁴ This causes potassium to enter the cell with glucose. The effects of the glucose and insulin can be noted within thirty minutes, and lasts about 6 to 8 hours. The calcium ion has a direct antagonistic effect to potassium ion on the heart and can be administered as 50 to 100 ml. of 10 per cent calcium gluconate solution.

Acidosis

One of the major functions of the kidney is to excrete the excess acid produced by routine metabolic processes.⁴¹ If kidney function is deranged, an accumulation of from 20 to 30 mEq. of hydrogen ions per day appears.^{18, 30} The hydrogen ion is derived from oxidation of sulfur-containing amino acids, phosphorus residues, and incompletely metabolized organic acids. The buffer systems of the body can usually maintain the CO₂-combining power around 17 to 19 mM. per liter, but if increased tissue breakdown is present, the CO₂-combining power will go below 12 mM. per liter, necessitating immediate treatment with alkali, or dialysis.³⁶

Table 1. *Emergency Treatment of Hyperkalemia*

SUBSTANCE	DOSE	ONSET OF ACTION	DURATION OF ACTION
<i>Prevention</i>			
Kayexalate	10-20 gm. dissolved in sorbitol, orally or rectally	1-2 hours	4-6 hours
Dietary restriction			
<i>Acute Hyperkalemia</i>			
Calcium gluconate	2-10 gm. intravenously	Minutes	30-60 minutes
Sodium bicarbonate	45-90 mEq. intravenously	Minutes	1-2 hours
Hypertonic glucose and insulin	25-50 gm. intravenously, 10-20 Units	Minutes	2-4 hours
Kayexalate	50-60 gm. dissolved in sorbitol, retention enema	30 minutes	4-6 hours

Congestive Heart Failure

Uremic pneumonitis and congestive heart failure usually reflect overhydration. In milder forms, fluid and sodium restriction plus digitalization may be adequate. (Care must be taken to prevent hypokalemia or hyperkalemia when using Digitalis preparations in order to prevent cardiac toxicity.) If overt pulmonary edema is present, the use of phlebotomy and rotating tourniquets before dialysis can be instituted may be life saving. Resistant pulmonary edema is a definite indication for dialysis.⁴ Peritoneal dialysis with the incorporation of hypertonic glucose solutions is the most efficient method of removing excess fluid, but hemodialysis with increased ultrafiltration is also effective.

Hypertension

Accelerated hypertension is a frequent and prominent finding in acute renal failure. The etiology may be sodium excess, fluid excess, or a glomerular or renal vascular lesion. Severe hypertensive encephalopathy is most often associated with lupus glomerulonephritis, necrotizing arteritis, polyarteritis nodosa, acute glomerulonephritis, chronic pyelonephritis, renal artery occlusion, and the accelerated phase of essential hypertension.³⁶ Antihypertensive drugs, such as methyl dopa, guanethidine, and hydralazine, may be necessary during the acute state, but the blood pressure can probably be controlled by restriction of fluid and sodium. The immediate use of intravenous trimethaphen or pentolinium with hydralazine may be necessary in malignant hypertension. Uremic patients may be hypersensitive to antihypertensive drugs, so a small test dose should be given (e.g., 10 mg. of guanethidine), 24 hours before gradually increasing the dosage.

Uremic Convulsions

Uremic convulsions are most frequently *grand mal* in type, but may have some Jacksonian features.⁴³ The appearance of convulsions in acute oliguric renal failure is considered a poor prognostic sign, but dialysis may reverse the process. Convulsions are generally preceded by muscle twitching and increased neuromuscular irritability, which does not respond to calcium infusion.⁴³ The muscle twitching and seizures usually respond to 30 to 50 mg. of secobarbital or amobarbital administered slowly intravenously. Five to 10 mg. of diazepam intravenously may also be used to control the acute seizures. Diphenylhydantoin in a dosage of 100 mg., three to four times per day, may be effective prophylactically.

Anemia

The cause of anemia in acute renal failure is unknown, but is probably related to the build-up of metabolic waste products. Studies have shown the red cell survival time to be shortened when the blood urea nitrogen is greater than 200 mg. per 100 ml., and that new cell formation decreases as the creatinine in the blood increases.⁴⁴ Usually the hemoglobin does not fall below 6 gm. per 100 ml., and transfusion is not necessary unless active bleeding is present. Ideally, the hematocrit should be

maintained between 25 and 30 per cent. If the hematocrit drops below 20 per cent and the patient is symptomatic (dyspnea, increased fatigue, weakness), packed cells should be given. Also, if the patient has angina pectoris the hemoglobin must be maintained above the critical level at which symptoms appear.

Infection

Overwhelming infection remains a common cause of death in acute oliguric renal failure.² In uremia, the host response is depressed, so that rapid recognition of an infection and prompt chemotherapy are necessary for the best possible outcome. One study showed an incidence of infection in 80 per cent of the cases—and infection as a direct cause of death in 14 per cent.⁹ Adequate aeration to all parts of the lungs may be improved by the use of simple balloon blowing, or more efficiently with the help of a physical therapist and breathing exercises.

Indwelling bladder catheters are notorious contributors to infections and their use should be limited. Coma, urinary retention, and the initial 24 hours of evaluation should be the only indications for the use of an indwelling catheter. If it must be left in place longer than 24 hours, a three-way bladder irrigation system using an antibiotic solution may decrease the incidence of systemic infection. Other preventive measures, such as early ambulation and good nursing care, help to prevent decubiti and resultant infections. If the patient has an arteriovenous shunt for hemodialysis, careful cleansing and proper care must be scrupulously carried out. Oral hygiene is also important in renal failure, since urea is excreted by the salivary glands, predisposing the area to stomatitis and parotitis if not properly cared for.

Acute oliguric renal failure may manifest a leukocytosis with a left shift and fever with pyuria, so the diagnosis of an early infection may be difficult. A high clinical suspicion plus frequent cultures must be relied upon to properly diagnose an indolent infection.

USE OF DRUGS IN PATIENTS WITH RENAL FAILURE

Antibiotics

When prescribing an antibiotic, its excretion and metabolism should be known. Colistin, streptomycin, kanamycin, gentamycin, tetracycline, polymyxin B, and amphotericin B are excreted mainly by the kidney. Thus their proper dosage is dependent on the glomerular filtration rate. Table 2 is a guide for a number of drugs used in acute renal failure; for more specific information concerning antibiotics, the reader is referred to the work by Kunin.²⁹ The appearance of respiratory depression following the use of colistin, kanamycin, polymyxin B, and streptomycin in renal failure has also been reported.³²

If long-term therapy with a drug excreted by the kidney is necessary, serum antibiotic levels are a useful adjunct. As a general rule, most antibiotics are not removed by dialysis, and the use of peritoneal or hemodialysis should not alter the regimen for patients in acute oliguric renal failure.

Table 2. *General Guide for Drug Administration in Acute Renal Failure*

TYPE OF DRUG	DRUGS REQUIRING REDUCED DOSAGE	DRUGS REQUIRING NO MODIFI- CATION OF DOSAGE
Antibiotics	Cephaloridine Gentamycin Sulfisoxazole Streptomycin Kanamycin Isoniazid Colistin Tetracycline Chlortetracycline Amphotericin Vancomycin Lincomycin	Penicillins Cephalothin Erythromycin Chloramphenicol Chloroquine
Cardiovascular drugs	Digitalis Procaine Quinidine Procainamide	Lidocaine Propranolol
Antihypertensive drugs	Alpha-methyldopa*	Furosemide Hydralazine Reserpine* Ganglionic blocking agents Guanethidine*
Barbiturates and tranquilizers	Phenobarbital Barbital Chlorpromazine* Prochlorperazine* Meprobamate*	Glutethimide Secobarbital Amobarbital Pentobarbital Thiopental Diazepam Chloral hydrate Paraldehyde
Anticonvulsives	Phenobarbital	Dephenylhydantoin (slight) Trimethadione (slight)
Narcotics and analgesics	Salicylates Phenylbutazone	Meperidine Codeine Morphine Propoxyphene Indomethacin

* Probable requirement based on available data.

Digitalis

Of the digitalis preparations, digoxin has the shortest half-life and is excreted mainly by the kidneys.²² Digitoxin, on the other hand, has a half-life of 6 days and is excreted mainly by the liver.²³ The loading dose of each drug remains the same in renal failure as with normal renal function; only the maintenance dose is decreased.

With anuria, the daily maintenance dose of digoxin is decreased from 35 to 14 per cent of the loading dose. Digitoxin, however, is only decreased from 13 to 7 per cent of the loading dose when anuria is present.

Sedation

For sedation, the short acting barbiturates—chloral hydrate and paraldehyde—may be used without dosage modification; but phenobarbital and barbital should be avoided. Of the tranquilizers, the phenothiazines and meprobamate must be reduced in dosage, whereas glutethimide and diazepam can be used at normal dosage levels.

Anesthesia

Major surgery is not contraindicated in acute renal failure if the patient is prepared with dialysis and special care is taken with hemostasis. The use of halothane, Thiopental, nitrous oxide, and succinylcholine for general anesthesia have shown to be quite effective.^{35, 38}

Analgesics

Salicylates and phenylbutazone should not be used for patients in acute renal failure, but meperidine, codeine, morphine, propoxyphene, and indomethacin may be used.

THE ROLE OF DIALYSIS IN MANAGEMENT OF ACUTE RENAL FAILURE

Dialysis is specific for the relief of the signs and symptoms of uremia. Early hemodialysis may prevent many complications of acute renal failure, and actually increases survival in post-traumatic patients.³⁷ In some patients, the clinical signs of uremia, (lethargy, neuromuscular hyperirritability, and anorexia) may appear with only moderate biochemical abnormalities, and early dialysis is necessary. On the other hand, there are patients in whom acute renal failure can be managed conservatively as outlined above. Most important, the use of dialysis should be used to supplement—not supersede—good medical and nursing management.⁴⁵ Specific indications for dialysis are outlined in Table 3.

Peritoneal dialysis and hemodialysis are equally effective in reversing the symptoms of uremia and in correcting abnormal fluid/electrolyte and acid/base balances. Peritoneal dialysis is safe and relatively simple, but carries some risk of infection.³⁴ This procedure is less efficient than hemodialysis for extraction of urea, creatinine, and other nitrogenous substances, but it is more efficient for removal of excessive fluid.

There is no absolute contraindication for peritoneal dialysis.⁴³ Hemodialysis is more effective in lowering the blood urea nitrogen and serum creatinine level and allows a greater flexibility in early ambulation.^{10, 26} However, extracorporeal dialysis is more dangerous in inexperienced hands; it requires general or regional heparinization, access to blood vessels, and may be unduly stressful to patients with bleeding tendencies or unstable blood pressure.

Table 3. *Indications for Dialysis in Acute Renal Failure*

Clinical indications

Uremia—Early signs of deterioration (anorexia, nausea, vomiting, mental confusion, muscle twitching, asterixis, convulsions) may be indications for early dialysis.

Overhydration—Congestive heart failure, pulmonary edema, refractory edema.

Biochemical indications

Uremia (Bun > 150 mg./100 ml.; serum creatinine > 15 mEq./L.)

Acidosis (Serum carbon dioxide < 15 mEq./L.)

Hyperkalemia unresponsive to conservative management

Either method of dialysis should benefit most patients with uremia due to acute renal failure. The methods are not mutually exclusive; both can be used in the same patient at different times for specific indications. The choice of therapy is often a matter of available facilities and personal preference.

MANAGEMENT OF THE PATIENT DURING THE DIURETIC PHASE OF ACUTE RENAL FAILURE

The major complications of the diuretic phase are dehydration, hyponatremia, and hypokalemia.¹¹ During the first few days, the urine output should be recorded and replaced every 6 to 8 hours. This can be done intravenously with 0.45 per cent saline plus potassium supplements, or orally with water, sodium chloride tablets, and potassium mixtures. The total insensible loss must also be replaced daily. Frequent determinations of serum electrolytes and body weights will help guard against dehydration and electrolyte abnormalities.

It is not unusual for the blood urea nitrogen to increase at the onset of diuresis, and occasionally a dialysis is necessary to relieve symptoms.

After 3 to 4 days, an attempt to decrease the urine output is made by replacing only 75 per cent of the urine volume. Care must be taken to prevent dehydration, but usually the urine output will decrease and the specific gravity will increase slightly. Tubular function then improves and sodium and potassium losses are curtailed. At this point, ad lib. fluids are usually sufficient, and if total recovery is to return, sodium supplements are not needed.

The last renal function to return to normal is the ability to concentrate the urine. This parameter can remain abnormal up to 6 months. If only partial recovery appears, long-term sodium supplements may be necessary. However, if hypertension is present, sodium depletion may help to control the hypertension. The diuretic phase must be followed actively and vigorously, for approximately 40 per cent of the fatalities appear during this period.⁹

SUMMARY

Acute oliguric renal failure is a catastrophic event and has a mortality of approximately 50 per cent.^{9, 27, 33} Mortality is directly related to

age, type of causative injury, and the presence or absence of underlying renal disease. All these factors must be assessed in each case; then, with the use of a few basic principles and constant vigilance, optimum results can be obtained.

Because the mortality and morbidity are so high in acute oliguric renal failure, every effort should be made to prevent its occurrence. This can be done by insuring adequate hydration and blood volume before and after surgery; using the proper diuretics at the onset of oliguria in any clinical situation; and being constantly aware of renal involvement in the many disease entities that can produce renal failure.

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Conservative Management of Chronic Renal Failure

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Conservative management of patients with chronic renal failure has increased in importance since intermittent dialysis and renal transplantation have become acceptable forms of medical and surgical therapy.

Our understanding of the pathophysiology of uremia and its complications has increased, dictating more rational and efficient therapy; patients with marked impairment of renal function can at times be maintained relatively symptom-free. Secondly, patients with "terminal" renal failure can be maintained in relatively good health by meticulous care. This is particularly valuable to those who may not benefit from dialysis or transplantation, owing to the overwhelming physical, emotional, and economic demands of these procedures.⁸⁷ For other patients, effective management delays the need for the more heroic forms of therapy. Thirdly, prolonged conservative management of renal failure allows the mental, social, and educational preparation of patients who will ultimately be treated by dialysis or transplantation or both, so that they become fully aware of the importance of their disease and the scheduled medical regimen.

DIFFERENTIAL DIAGNOSIS

"Chronic renal failure" is deterioration in renal function which progresses over a period of months or years toward a fatal termination due to uremia and its complications. The rate of this progress depends on the nature of the primary disease, the frequency of exacerbation, and the type and frequency of complications. The rate of clinical deterioration also depends on the quality of medical care.

In many cases of chronic renal disease, it is extremely difficult to

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Table 1. *Reversible Causes of Chronic Renal Failure*

<i>Obstruction:</i> Congenital—bladder neck obstruction, posterior valves, urethral strictures. Acquired—calculi, retroperitoneal fibrosis and ureteric fibrosis, ureteric granuloma, benign or malignant tumors encroaching upon the urinary tract, functional and reflex edema after retrogrades, functional bladder dysfunction in the debilitated, prostatic enlargement, urethral stricture.
<i>Infection of the urinary tract</i> (primary or secondary).
<i>Hypertension:</i> Essential, malignant, renovascular, pheochromocytoma, coarctation of the aorta.
<i>Subacute bacterial endocarditis.</i>
<i>Metabolic:</i> Hypercalcemia, hypokalemia, hyperuricemia.
<i>Hematological:</i> Multiple myeloma.
<i>Immunological:</i> Systemic lupus erythematosus, polyarteritis nodosa, Henoch-Schönlein purpura.
<i>Nephrotoxins and drugs:</i> Carbon tetrachloride, lead, bismuth, chronic analgesic abuse, hypervitaminosis D, mercury compounds.

identify the underlying cause. Despite this, an effort should be made to establish a diagnosis, to search for a readily correctable and remediable cause, and to exclude various factors which may have caused exacerbation of chronic renal disease. Tables 1 and 2 list some of these conditions, which are discussed in this paper.

Radiographic Examination

As can be inferred from Table 1, a thorough history, physical examination, routine screening studies, and urinalysis will often indicate the diagnosis of the underlying renal disease. Of particular importance in regard to prognosis and therapy is the assessment of kidney size, either by straight abdominal x-ray or with the aid of contrast media. Large kidneys in the presence of chronic renal failure may suggest diabetes mellitus, systemic sclerosis, amyloidosis, multiple myeloma, or a collagen disease such as systemic lupus erythematosus. The presence of normal sized kidneys, on the other hand, may suggest one of a number of reversible causes of chronic renal failure, and in these cases, renal biopsy is indicated to determine the diagnosis. Bilaterally contracted kidneys usually indicate an irreversible process, and renal biopsy is contraindicated, as in most cases the scarring and contracture of this "end-state" kidney will not allow a precise histological diagnosis. The radiographic examination may also be useful in excluding bilateral renal calculi and other forms of obstructive uropathy.

Table 2. *Aggravating Causes in Chronic Renal Failure*

<i>Cardiovascular:</i> Congestive cardiac failure, cardiac arrhythmia, hypotension (from hemorrhage or dehydration), hypertension.
<i>Metabolic:</i> Hyperuricemia, hypercalcemia, hypokalemia, hyponatremia and dehydration.
<i>Hematological:</i> Hemolysis.
<i>Infection:</i> Urinary, respiratory, gastrointestinal, systemic.
<i>Surgery and trauma.</i>
<i>Drugs and nephrotoxins.</i>

Pyelography

In the presence of renal failure, routine intravenous pyelography, with the standard preparation of dehydration and purgation, is contraindicated because of its deleterious effect on residual renal function. Further, certain patients with multiple myeloma^{17, 77} or diabetic nephropathy⁷⁸ have become acutely oliguric following dehydration and pyelography. In most cases the administration of a high-dosage contrast medium⁹⁰ or infusion pyelography is adequate to outline kidney size and to rule out urinary tract obstruction.^{86, 107} Delayed films at 6 to 24 hours after administration of contrast medium may be helpful, and tomography can also be utilized. If these methods give unsatisfactory films, renal function is probably nil and the patient is significantly uremic. A repeat infusion pyelogram following peritoneal dialysis may provide adequate visualization even when creatinine clearance is as low as 1 ml. per minute or less.⁶⁵ Rarely, retrograde pyelography may be required; otherwise, instrumentation should be avoided where possible as it carries the risk of infection, and an occasional patient may become oliguric due to obstruction caused by traumatic edema of the ureteric orifices.^{12, 47, 95}

REVERSIBLE CAUSES OF CHRONIC RENAL FAILURE

Obstructive Uropathy

Congenital deformities of the kidneys and urinary tract are usually associated with obstruction.^{53, 101} In the female, obstruction usually presents with recurrent infection at an early age. In the male, it may not be detected until a routine pre-employment physical examination, when hypertension and proteinuria are found. The adult with obstruction may have multiple symptoms arising from the urinary tract or may present only with uremia. Renal calculi, though usually symptomatic, may not be. Retroperitoneal or ureteric fibrosis is another correctable cause of chronic renal failure. The diagnosis is often suggested by displacement of the ureters on pyelography. These patients have no specific symptoms, but the history may reveal use of methysergide for migraine.^{84, 89}

Functional bladder neck obstruction occurs in the debilitated and aged from bladder overstretch. Overenthusiastic investigation is unnecessary, as catheter drainage for a few days will allow the bladder to regain its normal tone.²¹

Often, when urinary tract obstruction is relieved and any superimposed infection is treated, a surprising degree of renal function is restored. In severely ill patients with upper urinary tract obstruction, or obstruction along the urinary tract that cannot be circumvented by ureteric catheter, marked improvement can be achieved by percutaneous needle nephrostomy,⁷⁵ after which further investigation may be tolerated. This procedure has proved particularly useful in the aged, when heroic measures may only hasten their demise.

Infection

Infection, although treatable, accounts for almost 30 per cent of all deaths from renal causes in the United States.⁵⁷ With improved

methods of diagnosis and increased understanding in its management, urinary tract infection should not be permitted to progress into the chronic stage with production of renal failure.^{46, 102}

Hypertension

Significant hypertension, regardless of etiology, must be treated, because it brings about rapid deterioration in renal function. By the time chronic renal failure is evident, it is usually pointless to distinguish between renal parenchymal hypertension and essential hypertension, either of which may be complicated by malignant hypertension. However, removal of a pheochromocytoma or correction of coarctation of the aorta will certainly decrease the intensity of the vascular disease and simplify medical management. Despite some discouraging reports, surgical treatment of renovascular hypertension has been successful in younger people.

Subacute Bacterial Endocarditis

This disease affects the kidneys either directly, by what is believed to be an autoimmune process, or indirectly, when cardiac failure occurs. The lesion may be silent and smoldering and persist unsuspected. Clinically the diagnosis may be difficult because patients with renal disease often have functional cardiac murmurs and anemia too. Prognosis is relatively good, for renal impairment often regresses rapidly with effective treatment of the primary infection.

Nephrotoxic Drugs and Chemicals

Although chemicals such as carbon tetrachloride, lead, and bismuth usually cause acute renal failure, intoxication can occasionally produce chronic renal insufficiency.

Chronic analgesic abuse^{10, 28, 30} is now considered the commonest cause of aseptic pyuria in advanced countries. These patients are sometimes devious and deny such abuse; they are alleged to be psychoneurotics and may be recognized by their psychosomatic symptoms. Several reports have appeared of arrest of progressive renal damage when the analgesic was discontinued.

FACTORS CAUSING EXACERBATION OF CHRONIC RENAL FAILURE

Cardiac Conditions

These conditions may so reduce cardiac output that glomerular filtration is seriously lowered.²⁷ Scrupulous use of digitalis, diuretics, and antiarrhythmic agents can reverse congestive heart failure and thus significantly improve renal hemodynamics. Complications from over-diuresis or digoxin toxicity should be observed, as these may be mistaken for symptoms of renal failure.

Infections

Infections, however minor, cause exacerbations by increased catabolism with retention of metabolites and hyperkalemia. The choice of an antibiotic should depend on bacterial sensitivity, nephrotoxicity, route of excretion, and dialyzability. After the initial loading dose, subsequent dosage should depend on the level of the patient's glomerular filtration. Plasma assay of antibiotic levels may be needed.⁵⁴

Surgery and Trauma

Minor surgery or trauma, like infection, can bring about metabolic overload in a patient with precariously balanced renal function. Where possible, surgery should be deferred while the patient is appropriately prepared in regard to cardiovascular status, nutrition, and hydration.

Drugs

Any medication in chronic renal failure should be cautiously administered and with full knowledge of its complications, particularly when the drug is normally excreted by the kidneys. Any potential complication tends to be more severe and prolonged in the patient with renal insufficiency. Some complications are so similar to the symptoms and complications of renal failure that they are easily overlooked. Gastrointestinal symptoms may cause dehydration, and so further depress glomerular filtration; hematological complications aggravate those due to renal failure; catabolic or anti-anabolic effects of drugs like glucocorticoids or tetracycline^{25, 94} respectively will increase uremic symptoms, whereas diuretics may cause hyperuricemia. Some drugs like phenazopyridium³ cause further parenchymal damage where there is pre-existing renal insufficiency.

DIETARY MANAGEMENT IN CHRONIC RENAL FAILURE

For a long time dietary management in chronic renal failure meant a high-calorie, low-protein diet^{13, 18} which, though successful in reducing blood urea, was devastating in causing protein malnutrition. As patients were usually anorexic, they suffered calorie malnutrition as well. Since the work of Giordano³² and Giovannetti,³⁴ amply confirmed by Berlyne^{11, 29} and others, it is now well accepted that patients should have at least 18 gm. of protein per day of high biological value and calorie intake of 35 to 50 KCal. per kg. per day to prevent protein catabolism. Such patients not only have improved blood chemistries but are able to utilize their own blood urea³² and ammonia nitrogen⁸³ to synthesize nonessential aminoacids. Further there is marked general well being, disappearance of gastrointestinal symptoms and of uremic signs and symptoms, improved hemoglobin, and even possible prolongation of life.¹¹

This diet is best worked out between the patients, their responsible relatives, the dietitian, and the physician. The dietitian should have a directory of protein, carbohydrate, sodium, potassium, and water con-

tents of foods. She should know sources of supply of special foods and possess a store of recipes which will help to make meals more attractive and palatable. A 40 gm. protein diet may be prescribed if the creatinine clearance is over 10 ml. per minute, and a 20 gm. protein diet for a creatinine clearance of 2 to 5 ml. per minute. This diet aims at providing 0.25 to 0.5 gm. of protein of high biological value per kg. per day, derived mainly from eggs, milk, and lean meat. If the patient is on regular intermittent dialysis, the protein allowance is increased to 0.75 gm per kg. to maintain nitrogen balance.³¹ As this amount of protein represents a tremendous decrease from what most patients are accustomed to, every effort is made to reduce the intake of poor quality protein from starches and vegetables.

The results of the diet in those patients with sufficient residual renal function and who are able to cooperate have been extremely encouraging, though some fail to respond. Some patients require a few sessions of peritoneal dialysis to improve their general condition to enable them to retain their diet.^{48, 57} Others may harbor aggravating renal problems, such as hypertension, cardiac failure, or pyelonephritis, which, when treated, will enable them to be maintained on dietary treatment. When the creatinine clearance is less than 2 ml. per minute, the patient can hardly be expected to be sustained by dietary treatment alone.¹¹

Metabolic hyperkalemia and acidosis^{11, 29} may not be prevented by this diet. Sodium exchange resin or resins on calcium or aluminum exchange cycles may have to be used regularly to control hyperkalemia. Metabolic acidosis^{29, 64} may be corrected by giving the patient 5 gm. of calcium carbonate in divided doses daily, which also replenishes some of the low serum calcium. Patients on these diets also require supplements of B complex vitamins, particularly folic acids.

Clinically the criteria for adequate dietary control include general well being without uremic symptoms, steady muscle increase, steady hemoglobin level, and full rehabilitation. Biochemically, the blood urea nitrogen should not swing unduly and is best maintained at about 60 mg. per 100 ml. Serum proteins should rise, with an albumin level of over 3.5 gm. per 100 ml. Serum electrolytes, iron, calcium, and phosphorus levels should be controlled near normal. With stress, such as surgery or infections, additional dietary allowance is necessary and dialysis may be needed frequently.^{11, 29, 36, 57}

MANAGEMENT OF WATER AND ELECTROLYTE DISTURBANCES

Acidosis

Acidosis^{82, 91} in chronic renal failure is due to the inability of the kidney to excrete nonvolatile acids, to produce ammonia, and, in some cases, to conserve bicarbonate. Plasma bicarbonate levels may stabilize at about 16 to 18 mEq. per liter, thus leaving very little reserve for sudden acid loads; levels below 15 mEq. per liter usually give rise to symptoms.

Full correction is impracticable and also carries the risk of tetany;

the use of sodium buffers may cause circulatory overload and hypertension. For moderate acidosis, calcium carbonate,⁶⁴ 5 gm. per day in divided doses, is effective, and the use of sodium bicarbonate can be avoided. Sodium bicarbonate is used in preference to other agents in severe acidosis, but when water overload is an added problem, dialysis is the safest and most effective way of correcting both disorders.

Salt and Water

Salt and water depletion results from failure of the diseased kidneys to conserve sodium. This may occur in any renal disease but is more common in chronic pyelonephritis and other renal medullary diseases. Patients are dehydrated, complain of cramps, and have a low or normal blood pressure. Urinary sodium is excessive despite low serum sodium concentrations. Terminally, glomerular filtration may be so low that the tubules are capable of reabsorbing all filtered sodium. Oral sodium replacement may be adequate, but in severely depleted patients intravenous hypertonic saline (3 to 5 per cent) may be needed. In addition, these patients usually have severe metabolic acidosis, and sodium bicarbonate should be used to replace part of the sodium deficit. Marked clinical and biochemical improvement results when adequate salt and water is replaced.

After the initial deficit is corrected, daily sodium requirement should be determined after a period of sodium balance studies and daily weights. An adequate amount of fluid is required to excrete the metabolic wastes, but sodium retainers rapidly retain water and develop edema, hypertension, and congestive cardiac failure. Their sodium intake must be reduced accordingly. If fluid retention occurs despite this, water restriction to 500 ml. (equal to insensible fluid loss) plus a volume equivalent to the previous day's urinary output should maintain the patient within balance. The patient should weigh himself at the same time each day, preferably before breakfast, after voiding. Any weight increase or decrease of over 1 kg. would indicate overload or depletion.

Hyperkalemia and Hypokalemia

The kidney has a remarkable reserve for increasing potassium excretion: hyperkalemia is encountered persistently only when urinary output is reduced to less than 250 ml. per day.³² Patients with renal failure are unable to deal with sudden potassium loads, so that they should always observe some potassium restriction and catabolic situations should be promptly treated.

Moderate hyperkalemia, to about 5 to 6 mEq. per liter, without symptoms or electrocardiographic changes, may require no treatment except observation. Hyperkalemia of about 6 to 7 mEq. per liter should be treated promptly with intravenous glucose and insulin (20 gm. of glucose with 10 units of soluble insulin if fluid overload is a danger; otherwise 1 liter of 10 per cent glucose with 50 units of soluble insulin) or with 100 to 300 mEq. of sodium bicarbonate. Calcium gluconate may be used to protect the myocardium from the direct cardiotoxic effects of hyperkalemia. As a more permanent measure, potassium can be removed with sodium exchange resins. Kayexalate (sodium polystyrene sulfonate) can be

given in 50 gm. doses at 6 hour intervals together with 20 ml. of 70 per cent Sorbitol. Resin enemas with Sorbitol can be used for those unable to swallow or retain oral fluids. Peritoneal dialysis or hemodialysis is indicated when severe signs and symptoms of potassium intoxication are combined with fluid overload.

Hypokalemia may occur in renal potassium wasting, in overcorrection of hyperkalemia along with loss of gastrointestinal fluids, or during dialysis with potassium-free dialysates. Hypokalemia should be carefully watched for when the patient is receiving cardiac glycosides.

Magnesium

Magnesium intoxication is uncommon in clinical practice²⁰ and occurs only when a patient has ingested magnesium compounds, such as antacids or purgatives, for some time. Nonspecific signs like hypotension and nausea may appear before the more characteristic symptom of central nervous system depression.⁸¹ Hypermagnesemia may be treated by intravenous calcium infusion or dialysis.

Hypomagnesemia⁴⁰ sometimes occurs from prolonged low intake and gastrointestinal loss and is manifested by central nervous system hyperirritability ranging from tremors to convulsions. It probably occurs most commonly during dialysis using magnesium-free solutions. Hypomagnesemia should be avoided, because it may be a potential stimulus to parathyroid hormone secretion.⁶³

PREVENTION AND TREATMENT OF BONE COMPLICATIONS

Vitamin D resistance occurs very early in renal insufficiency, while creatinine clearance is still at 70 per cent of normal.^{58, 97} This may be the result of abnormal metabolism⁶ of the vitamin, either by increased destruction of the active component or by true resistance at its effector sites.^{60, 109} The result is decreased gastrointestinal absorption of calcium and phosphates and defective mineralization of cartilage and bony matrix, resulting in osteomalacia. Decreased sensitivity of bone to the action of parathyroid hormone may result in further hyperparathyroidism.

Hyperphosphatemia may be the earliest change in chronic renal failure causing hypocalcemia.¹¹ It is due to decreased tubular excretion, lean tissue breakdown from starvation, use of catabolic agents like glucocorticoids and tetracyclines, or dietary intake. Parathyroid hormone secretion increases, restoring tubular secretion of phosphates toward normal as long as the creatinine clearance exceeds 20 to 30 ml. per minute.³⁵ With lower creatinine clearances, glomerular filtration is inadequate to handle the increased phosphate load. Serum phosphorus is further augmented by excessive bone resorption under the action of parathyroid hormone.

The ionized calcium concentration is inversely related to the level of inorganic phosphate in the normal person and in the early stages of renal failure. It is also dependent on intestinal absorption of calcium,

on changes in pH, on albumin binding, and on the amount of complex calcium formed. Parathyroid activity is most sensitive to the level of serum ionized calcium, and prolonged stimulation of the parathyroid glands results in hyperplasia and ultimately in autonomy of function. Secondary hyperparathyroidism presents with bone destruction ranging from subperiosteal bone resorption to osteitis fibrosa. When both calcium and phosphate (particularly phosphate) levels are raised and the $\text{Ca} \times \text{P}$ product is above 75, there is an increased tendency to soft tissue calcification, primarily in the cornea and conjunctivae, walls of arteries, joints, skin, and viscera.

Management of calcium metabolism in chronic renal failure is difficult in that one can never be sure what is happening at a particular time; random measurements of calcium and phosphorus do not depict the underlying pathophysiology. Stanbury⁹⁹ has emphasized the importance of treating the patient rather than his biochemistry or our hypotheses. That is, management can be successful only with full knowledge of the clinical condition, metabolic balance studies, and bone pathology (by bone biopsy). Calcium, phosphorus, and alkaline phosphatase levels, together with bone x-rays, are followed as a guide to therapeutic maneuvers and to progress. The objective of therapy is straightforward, but in practice it is hard to achieve. It is to maintain as near normal levels of calcium and phosphorus as possible, thereby preserving the skeleton and preventing extraosseous calcification.

In early renal failure, hyperphosphatemia may be prevented by reducing phosphates (along with protein) in the diet and by the use of antacids such as aluminum hydroxide. Magnesium compounds are undesirable for fear of hypermagnesemia. Hypophosphatemia⁶² is to be avoided because it gives rise to uremic-like symptoms per se, and it may result in reciprocal hypercalcemia,⁵⁰ particularly if the patient is also receiving vitamin D or has secondary hyperparathyroidism. As calcium and phosphorus can only be absorbed from the gut on a one-to-one molar basis, excess antacids may also prevent proper absorption of calcium. Bone mineralization cannot proceed while there are insufficient phosphates, and in fact, calcium becomes mobilized from bone into the extracellular space, resulting in osteoporosis and osteomalacia.

Serum calcium levels may be improved by increasing oral calcium intake.⁶⁴ Calcium carbonate, 10 to 20 gm. per day, is popular because it supplies calcium and also reduces acidosis.⁵⁵ Extreme fluctuations of pH are best avoided: alkalosis may cause tetany, which may precipitate fractures; acidosis increases ionized calcium and at an undesirable period, when serum calcium is high and vitamin D resistance low, may result in soft tissue calcification.

Vitamin D therapy^{98, 100} is indicated when defective mineralization occurs. The degree of vitamin D resistance varies, and the initial dose should be 10,000 to 20,000 units daily. This is slowly increased over a 3 or 4 week period until the desired effect is obtained (occasionally 10 to 50 times the usual dose is required). It is imperative to monitor calcium, phosphorus, and alkaline phosphatase levels closely. The first sign of response to vitamin D therapy may be a rise of phosphate level. When

protein intake is adequate, bone pains cease, bone mineralization and healing occur, and calcium may now be mobilized from soft tissues. As calcium level rises, parathyroid hormone production should decrease and the renal osteodystrophy syndrome should be corrected. At this stage, vitamin D therapy may be discontinued, to be restarted when warranted. Even when there is slight parathyroid autonomy with mild osteitis, good results may be obtained with phosphate regulation and vitamin D therapy.⁹⁹

When osteitis fibrosa is more generalized and the calcium $\times$ phosphate product is already above 75, vitamin D should not be used; these patients require subtotal parathyroidectomy. This procedure has also been recommended for intractable pruritus and vascular calcification if it involves blood vessels required for renal transplantation. Total parathyroidectomy should be avoided, as hypoparathyroidism is extremely difficult to manage. Calcitonin^{60, 80} has been used successfully in hypercalcemia of metastatic tumors and in metastatic parathyroid carcinoma, but not in secondary hyperparathyroidism of renal failure. There is evidence that magnesium may inhibit parathyroid secretion, whereas decreased magnesium stimulates it, so that in certain centers, care in maintaining normal magnesium levels has been identified as one of the factors preventing soft tissue calcification.⁴⁹

Osteosclerosis is a symptomless bone disorder in chronic renal disease; there is an increase in demineralized and mineralized matrix in any part of the skeleton. There may be increased radiological density in the bones, particularly the end plates of the vertebrae and the metaphyses of long bones. The cause is unclear and there is no treatment.^{98, 100}

Arthritis

Arthritis and peri arthritis⁷⁶ in chronic renal failure is generally due to pseudogout type 2, characterized by pain and swelling in single large joints which contain milky, later thick, fluid with hydroxyapatite microcrystals but little calcium or uric acid and no calcium pyrophosphate dihydrate crystals of pseudogout type 1. Calcification of periarticular tissues follows the pain. Pseudogout type 2 responds to colchicine. Swelling and radiological changes disappear after lowering of serum phosphates, but dialysis is of debatable value.^{69, 76}

Typical clinical gout is uncommon in chronic renal failure, but hyperuricemia, which is common, is best prevented by allopurinol—not more than 300 mg. per day—if the patient is not already on dialysis. Clinical gout is sometimes a manifestation of secondary hyperparathyroidism.⁷⁶

PREVENTION AND MANAGEMENT OF CARDIORESPIRATORY COMPLICATIONS

Patients with prolonged uremia may develop cardiomyopathy, which fortunately may be reversed by diet and dialysis.⁷ Hypertension may be prolonged and difficult to treat. Anemia causes hyperdynamic circulation which is aggravated in those with large internal arteriovenous fistulas placed for hemodialysis.

Treatment of congestive cardiac failure is initially conservative, using diuretics and digoxin. However, most diuretics are ineffective in renal failure and they have many side effects.^{13, 71} Only furosemide and ethacrynic acid have been effective in large parenteral doses, but transient and permanent deafness have resulted from the use of the latter.⁷⁹ Furosemide may be given intravenously in progressively large doses up to 2 gm. per day and produces brisk diuresis even when creatinine clearance is as low as 5 to 6 ml. per minute. Oxygen and morphine (15 mg.) are valuable adjuncts in management.

Digoxin is used only when the above measures fail, for its response is uncertain, its toxicity is frequent,⁸⁵ and it cannot be easily dialysed. However, it is still very effective when the dose is carefully regulated. Most patients can tolerate half the usual loading dose and a quarter of the daily maintenance dose, but extreme variations occur.^{1, 24, 15} Nausea and vomiting, the earliest toxic symptoms, may easily be mistaken for symptoms of uremia. Potassium depletion should be looked for, particularly when gastrointestinal symptoms occur and when diuretics are used. Peritoneal dialysis or hemodialysis is the answer in the difficult patient with severe congestion and minimal renal function.

Pericarditis^{1, 9} may be symptomless, recognized only by the presence of biphasic precordial friction sounds. Such patients should be followed closely for pericardial effusions and tamponade, recognizing the fact that typical signs and electrocardiographic findings may not appear and an echocardiogram or scintiscan may be needed. Pericarditis may subside with better control of the uremic state by diet and dialysis. Effusions require aspiration only when symptomatic. Recurrent symptomatic effusions and tamponades may be difficult to control, requiring surgical drainage and creation of a pericardiopleural window.

It is difficult to know whether the bleeding tendency of uremia, prolongation of life with hemodialysis, or the use of heparin have caused the increased incidence of pericardial complications.⁷³ Many effusions become hemorrhagic, and recurrent sanguinous effusions may result in fibrous constrictive pericarditis severe enough to demand surgical treatment.⁶⁸

Uremic pneumonitis is due to defective capillary permeability, so that pulmonary edema occurs easily. Pleuritis⁷⁴ and serosanguinous effusions are less frequently seen; these may run the same course as pericardial effusions and cause respiratory insufficiency from restrictive disease.

Some patients, particularly women, for obscure reasons, develop distressingly massive ascites without peripheral edema. The mechanical impediment to respiration often demands relief by aspiration, but this carries the risks of enormous protein loss and rapid refilling. These patients have responded to fluid and dietary restrictions, intravenous salt-free albumin infusions, and vigorous dialysis.

Hypertension

Most renal diseases, especially in the end stages, are complicated by hypertension, which may be malignant and accompanied by severe cardiac and cerebral symptoms. Prompt treatment and maintenance of ade-

quate renal output has improved renal function and increased survival.⁷⁰ In malignant hypertension, intramuscular hexamethonium, reserpine, or hydralazine is customarily used but not always successful. Diazoxide^{38, 70} can be very effective in resistant cases and is given intravenously in 300 mg. doses repeated once or twice. Patients should be recumbent during this treatment to avoid the sudden disastrous effect of hypotension. Other potent drugs are trimethopran and nitroprusside. For moderate hypertension methyl dopa is preferred as it has less sudden severe side effects. Guanethidine or hydralazine is added in difficult cases. In all azotemic patients, dosage increase or addition of a second antihypertensive agent should be done gradually to avoid cumulative effects and sudden severe hypotension.

The aim in antihypertensive therapy is a diastolic pressure of 105 to 110 mm. Hg. This may be difficult to achieve without salt and water restriction.²² Furosemide is usually required to obtain a urinary output of 1 liter a day.⁷⁰ As renal disease advances, salt and water restriction becomes increasingly difficult and hypertension becomes impossible to control by conservative means without the use of long-term dialysis.^{22, 41} With dialysis, many patients have been able to stop antihypertensive medication completely. Some require modest doses of antihypertensives, while others fail to respond. This latter group produces tremendous amounts of renin in response to the severe salt depletion from salt restriction and dialysis. The renin is most probably the cause of their hypertension, because their blood pressure problems generally cease after bilateral nephrectomy removes the major source of renin.^{16, 106} Successful renal transplantation is the most reliable and logical method of restoring the blood pressure.⁵¹

Anemia

Patients in chronic renal failure tolerate anemia remarkably well, and there is little evidence that manipulation of hematocrit will improve renal function.^{15, 66} In fact it is impossible to maintain a normal hematocrit for any practical length of time due to increased hemolysis related to an extravascular substance, methylurea.^{19, 33} Repeated transfusion or overenthusiastic iron therapy carries a definite danger of iron overload.^{39, 96} A high hematocrit may suppress hemopoiesis;^{2, 72} transfusion increases the risk of hepatitis⁶¹ and may introduce tissue antigens, complicating subsequent transplantations.¹⁰⁸

Blood transfusion is indicated only when distressing symptoms of anemia arise; in the elderly, where angina pectoris, peripheral vascular insufficiency, or cerebral ischemia are potential hazards; in those with severe infections; or in those undergoing surgery. A hematocrit of 25 to 30 per cent is sufficient.

When uremia is controlled by diet or adequate dialysis, significant improvement in the hemoglobin level results, thus reducing the need for transfusion.^{11, 29} This is hypothesized to be due to increased general well being, permitting adequate dietary intake and removal of toxic substances that depress the marrow or cause persistent occult bleeding. Some patients, especially those on dialysis, despite the diet, become

depleted of folates²⁸ and iron.² The latter event results from low dietary iron, improved erythropoiesis, and a constant, though small, loss of blood in the dialysis machine. Folate supplementation should be routine, and oral or parenteral iron may be needed when the serum iron is low. Cobalt salts² are no longer recommended, because of troublesome gastrointestinal effects; androgens, however, may yet prove valuable in stimulating erythropoietin production even in the anephric patient.²³

Neurological Complications

Patients in severe uremia may have intellectual and psychological impairment, sleep disturbances, or neurological deficits^{104, 105} that may potentially exclude them from consideration for long-term dialysis or transplantation. Much improvement may result from dialysis and strict dietary control; the uremic state should always be improved before any decision regarding the patient's long-term management is pronounced.

Residual psychological disturbances require tremendous patience and cooperation from the patient, his relatives, the medical staff, and the psychiatrist. Insomnia may last for days and cause much anxiety. Some patients get some respite the night of dialysis and depend on hypnotics or sedatives in the intervening days. Drugs not excreted by the kidneys, such as chloral hydrate, barbiturates, or paraldehyde, should be used first. Noludar and diazepam are useful second line hypnotics. Sometimes judicious combination of sedatives, hypnotics, and alcohol may be required.

Convulsions are not an uncommon cause of death. They may be related to sudden hypertensive episodes due to salt and water overload, or localized seizures may be due to small foci of cerebral necrosis, hemorrhage, and fibrosis.¹⁰⁴ Penicillin¹² in large doses can cause convulsions in patients with renal insufficiency. Organic lesions should be excluded in patients who are otherwise stabilized; a patient with polycystic kidneys may have a ruptured cerebral aneurysm.³⁷ Patients on hemodialysis, because of anticoagulation, may have a greater bleeding tendency and present with convulsions from subdural hematomas.^{56, 88} Wernicke's encephalopathy has been seen in malnourished patients. Convulsion-prone patients should be treated with long-term anticonvulsants, such as diphenylhydantoin.

Sensory and motor neuropathy^{44, 52, 103} may be sufficiently debilitating to prevent full rehabilitation. Sensory disturbances begin symmetrically and distally and migrate proximally. Motor defects, such as impaired reflexes, muscular weakness, or paralysis, appear later and may begin proximally and remain localized. Objectively, delayed nerve conduction or posterior column changes usually precede subjective sensory symptoms, so that detection of these and institution of dialysis may prevent full-blown symptoms in many patients. However, dialysis may not improve motor function. Patients who develop neuropathy only after the start of dialysis may have concurrent severe catabolism arising from infections or surgery, signifying the need for more intensive dialysis. Vitamins have not helped, but transplantation has consistently brought

about relief. Nitrofurantoin^{5, 25} has been reported to cause fatal neuropathy; triamcinolone and cycloserine should also be avoided.

Asterixis, fasciculations, and muscle spasms bedevil some patients and are difficult to suppress. An abnormal calcium:potassium ratio has been noticed but cannot be incriminated.¹⁰⁴ Alterations in serum magnesium levels sufficient to cause central nervous system symptoms are uncommon; although decreased intracellular magnesium is observed, these patients do not have involuntary movements.⁵⁹ The role of other divalent ions is unclear. Many of these patients are relieved by dialysis.

MANAGEMENT OF THE SURGICAL PATIENT

As lives are prolonged by better medical care, some patients with chronic renal disease may require surgery for unrelated problems, or nephrectomy, or transplantation. The basic condition requiring surgery may already have pushed the patient to the verge of overt uremia and if uncorrected, surgical trauma may precipitate further complications because of increased catabolism, hypotension with further depression of glomerular filtration, overhydration which may precipitate cardiac failure and hypertension, bleeding tendencies from uremia, neuropathy,¹⁰³ or bacterial infection which is increased with undernutrition.⁹³

The following scheme is useful before surgery.

1. The hematocrit should be 25 to 30 per cent. If a blood transfusion is required, the potassium level should be observed.
2. Urea nitrogen, should not exceed 100 mg. per 100 ml., creatinine should not exceed 10 mg. per 100 ml., and potassium should not be over 5.5 mEq. per liter.
3. Bleeding and clotting defects should be corrected.
4. Blood pressure should be controlled.
5. Those who respond to diuretics may benefit from administration of furosemide intravenously (200 to 1000 mg. every 6 hours) starting 12 hours before surgery.⁸ Dehydration or hypokalemia must be avoided.
6. Peritoneal dialysis or hemodialysis may be required to correct any of the above defects.

Care After Surgery

Potassium should be checked every 12 hours and hyperkalemia corrected by oral or rectal sodium exchange resin, or by dialysis with an electrocardiogram as a guide. Check blood urea nitrogen, electrolytes, and creatinine daily. For fluid balance, administer a minimum of 500 ml. plus the previous day's urinary output. Continue intravenous furosemide in the patient who responds preoperatively.

Weigh the patient daily. Aim at loss of 0.5 to 1 kg. per day, since the patient on minimal caloric intake is expected to lose weight.⁶⁷ Give adequate calories—at least 100 gm. of carbohydrate per day to obtain a protein-sparing effect. This may be given as 500 ml. of 20 per cent glucose or dextrose. As soon as oral intake is possible, a liberal diet is necessary to hasten recovery. Patients without satisfactory renal output, or those who are nutritionally deprived, may require hyperalimentation with amino acids and glucose. Daily peritoneal dialysis or hemodialysis may be

needed for this. The patient who is already on hemodialysis invariably requires dialysis a day before, and usually daily for 4 or 5 days after, a major operation, depending on the diet and the biochemical changes.

CONCLUSION

With medical assistance, the patient with progressive chronic renal failure can walk the tenuous tightrope for a longer time without falling to one side (insufficiency) or the other (excess); both sides are fatal. When this is no longer possible, he requires long-term dialysis or transplantation, or he dies.

Long-term dialysis is recommended (1) when glomerular filtration is less than 1 or 2 ml. per minute and the patient cannot survive on the 18 to 20 gm. protein diet without symptoms; (2) when there are persistent symptoms from uremia; a BUN exceeding 150 mg. per 100 ml., creatinine over 15 mg. per 100 ml., potassium above 6 mEq. per liter, and plasma bicarbonate less than 16 mEq. per liter, despite good dietary control; in the presence of persistent edema, hyponatremia, hypertension, and congestive cardiac failure; and when there is peripheral neuropathy or multiple and frequent complications.

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Peritoneal Dialysis and Hemodialysis

*George Dunea, M.B., M.R.C.P. (Lond., Edin.)**

Gradually the idea grew in me that if we could only remove 20 g. of urea and other retention products per day we might relieve this man's nausea, and that if we did this from day to day life might still be possible. This was in 1938 . . .

WILLEM J. KOLFF

Within three decades dialysis has revolutioned the field of nephrology and opened new vistas in the treatment of uremia. This remarkable development was made possible by the efforts of a handful of pioneers who overcame obstacles that often seemed insurmountable. At first, progress was slow and disappointments were frequent. Yet, dialysis gradually outgrew its difficult beginnings and became established among the great medical achievements of our age.

PERITONEAL DIALYSIS

Peritoneal dialysis has become a simple procedure which is now available in most hospitals.^{1, 2, 11} It is done with commercially prepared solutions and disposable catheters,⁷¹ is easy to set up, and carries a low incidence of complications.

GENERAL PRINCIPLES

The peritoneal cavity is lined by a semipermeable membrane which has an area of about 2.2 square meters. Water and its solutes are transported across this membrane, mainly by diffusion. Urea is cleared at a rate of about 15 to 30 ml. per minute. Creatinine, a substance of larger molecular size, is cleared more slowly, at 10 to 15 ml. per minute.

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The clearance of a solute such as urea depends on a number of factors:

EQUILIBRATION TIME. When fluid is introduced into the peritoneal cavity, urea diffuses rapidly for the first 30 minutes and then more slowly for the following 2 hours.

RATE OF DIALYSATE FLOW. When the flow of the dialyzing fluid is increased from 1 liter to 3.5 liters per hour, urea clearance increases from 12 ml. per minute to 30 ml. per minute. Further increments in clearance may be obtained with higher flow rates. For example at flow rates of 12 liters per hour, urea clearance may be as high as 55 ml. per minute.⁶⁸ Such flow rates are hard to achieve in clinical practice, and the cost of the fluid would be prohibitive.

TEMPERATURE. Heating dialysis fluid from 20 to 37° C causes dilatation of peritoneal vessels and increases urea clearance by 35 per cent.²⁴

DIALYZING FLUID. Hypertonic solutions increase urea transport because of solvent drag and increased permeability of the peritoneal membrane. The use of 7 per cent instead of 1.5 per cent glucose concentration in the dialysis fluid increases urea clearance by about 50 per cent.²⁸

PERMEABILITY OF THE PERITONEUM. This is increased by heat, hypertonic solutions, infection, and experimentally by surface-active agents such as dioctyl sodium sulfosuccinate. Decreased permeability to creatinine, urate, and other larger molecules may occur in the acute renal failure associated with heat stress and exercise.⁴⁵

PROCEDURE

Peritoneal dialysis is usually done with commercially available administration sets and solutions, and with a disposable thin-tylet cannula which is inserted percutaneously.⁷¹ Some physicians distend the abdomen with 2 liters of dialysate through a No. 13 needle, but this is not necessary.

The patient's bladder is emptied and the patient is weighed. The cannula is inserted under local anesthesia at a midline site about 2 to 3 inches below the umbilicus. It is helpful if the patient raises his head at the moment of insertion to tighten the abdominal muscles and prevent perforation of the bowel. A feeling of "give" indicates that the peritoneal cavity has been entered. The tyset is then removed. The cannula is advanced toward the left pelvic gutter, fixed with sutures and tape, and connected to the dialysis bottles.

The dialysis is conducted by nurses. Two liters of warmed dialysate are run into the peritoneal cavity, allowed to remain for 30 minutes, and then drained out. The entire cycle is conveniently timed to last 1 hour. For a more rapid dialysis the equilibration time may be shortened so that the cycle is reduced to 45 or even 30 minutes;⁴¹ however, this requires more fluid and increases costs. Dialysis time is usually limited to 48 hours. The cannula is then removed, but may be reinserted later if necessary.

A dialysis fluid potassium concentration of 2 mEq. per liter is generally used, but in hyperkalemic patients, potassium should be omitted for about 10 exchanges. In digitalized patients, serious arrhythmias may occur if the potassium level is lowered too quickly, and a potassium concentration of 4 mEq. per liter is therefore recommended.

Hypertonic solutions (4.5 or 7 per cent glucose) may be used to remove fluid in overhydrated patients. A careful record must be kept of the patient's weight and of the amount of fluid exchanged, to prevent hypovolemia. A central venous catheter is sometimes needed.

During dialysis, the patient usually takes an unrestricted diet and is encouraged to sit in a chair. He should be examined frequently to detect arrhythmias, respiratory complications, overhydration, and peritonitis. Systemic infection is treated with the appropriate antibiotics. Most antibiotics are poorly removed by peritoneal dialysis. Minor dosage adjustments may be needed for kanamycin and colistimethate.

COMPLICATIONS

Although the course of peritoneal dialysis is usually uneventful, many complications have been described.^{1, 2, 41, 52}

Abdominal pain and discomfort occurs most frequently in the early stages of the dialysis. Local injection of procaine may be tried, but systemic analgesics are more effective. Discomfort may sometimes be alleviated by using only 1 liter of fluid for each exchange.

Drainage problems may be due to faulty positioning of the cannula, blockage of the cannula by fibrin or omentum, an air-lock, loculation of fluid, or an inadequate reservoir of fluid in the peritoneal cavity. It is often helpful to leave 1 to 2 liters of fluid in the peritoneal cavity instead of attempting to recover the fluid in its entirety.^{1, 2} Sometimes the cannula has to be irrigated with heparinized saline, repositioned, or replaced.

Extravasation of small amounts of fluid is of little consequence, but occasionally large volumes may dissect into the subcutaneous tissues. This seems to occur mainly when the abdomen has been distended by means of a needle prior to cannula insertion.

Bleeding or leakage around the puncture site can generally be remedied by the use of additional sutures. Fatal hemorrhage has occurred in one patient following accidental rupture of a mesenteric vessel.

Peritonitis occurs in 5 to 10 per cent of dialyses and is usually caused by gram-negative organisms or *Staphylococcus aureus*.^{2, 41} In recent years it has become less frequent because of better cannulas, shorter dialysis time, and improved asepsis.⁵⁸ Antibiotics are not routinely added to the dialysis fluid. Peritonitis is usually treated with systemic antibiotics.

Intraperitoneal administration of antibiotics has been recommended because high local levels of antibiotic are achieved. However, most antibiotics are also rapidly absorbed from the peritoneal cavity, and high blood levels may also be obtained.

Perforation of the bladder is a rare accident and can be avoided by emptying the bladder before dialysis.

Perforation of the bowel is uncommon but is more likely to occur when intra-abdominal adhesions are present. It may occur late in the course of dialysis, apparently because of pressure of the cannula on edematous bowel.⁵⁵ Diagnostic criteria include retention of dialyzing fluid in the abdomen, massive watery diarrhea, or return of cloudy, malodorous or feculent fluid.⁵⁵ Immediate laparotomy is necessary. Dialysis may be continued if a cannula is placed in the peritoneal cavity at the time of surgery.

Wound evisceration and omental herniation have occurred following operation, or with surgical insertion of cannulas, but not with use of the stylet-cannula.

Loss of the cannula into the peritoneal cavity may occur if the cannula is not well fixed to the abdominal wall. Confused patients have also been known to pull out cannulas.

Overhydration or hypotension result from poor control of fluid balance. Patients should be weighed frequently, and an accurate record of the volumes of fluid exchanged should be kept.

Pulmonary complications include atelectasis, pneumonia, and purulent bronchitis.⁵ They are related to upward displacement of the diaphragm and shallow respirations, and may be partially prevented by using more rapid 1 liter fluid cycles and by elevating the head of the bed. Effusions occur when fluid passes into the pleural cavity through openings in the diaphragm.

Pulmonary edema and heart failure are due to overhydration, severe hypertension, or pre-existing cardiac damage. Elevation of the diaphragm, poor perfusion of the lung bases, increased cardiac output, and pulmonary hypertension are further contributing factors.⁶⁵ Use of small amounts of hypertonic solution (1 liter of 7 per cent glucose) per cycle is helpful.

Protein loss occurs to the extent of as much as 20 to 60 gm. of protein and 5 to 10 gm. of amino acids, depending on the duration of dialysis.⁴

Hypernatremia may occur when hypertonic solutions are used, because water is removed more rapidly than sodium.⁴⁴

Hyperosmolar nonketotic coma with a precipitous rise in blood sugar may occur in diabetics and produce progressive deterioration in the level of consciousness and coma.

Lactic acidosis has occurred in patients with hepatic insufficiency because of failure to metabolize the lactate contained in the dialysis fluid to bicarbonate.

INDICATIONS

Peritoneal dialysis is commonly used in the treatment of acute renal failure. It has been used to treat patients with "hypercatabolic" renal failure,⁸ but most physicians prefer hemodialysis in this situation. It is valuable in preparing patients for surgery or diagnostic procedures, and has been used successfully in infants.

Patients with chronic renal failure have been maintained successfully for over 3 years with peritoneal dialysis. This procedure is particularly useful in the treatment of small patients who have some residual urine output and who need only occasional dialyses. It is less effective for regular maintenance dialysis, but has been employed successfully, even in the home.⁶⁶

There are relatively few contraindications to peritoneal dialysis. Difficulties may arise in patients with extensive abdominal trauma, surgery, or infection. Insertion of a cannula may be technically difficult when patients are obese or have postoperative adhesions. The only absolute contraindication to peritoneal dialysis is a patent opening in the diaphragm.

Although peritoneal dialysis is only about one fifth as effective as hemodialysis, it may be preferred when large amounts of fluid must be removed or when anticoagulation, cannulation of blood vessels, or sudden changes in electrolyte balance or blood volume are undesirable. Peritoneal dialysis has also been used to treat poisoning, hypercalcemia, congestive heart failure, peritonitis, pancreatitis, and hepatic coma.

VARIATIONS OF TECHNIQUE

A standard procedure is used in most hospitals, but many variations in technique are possible.

Equipment can be varied. Some units prefer larger cannulas to obtain better flow. Such cannulas must be inserted surgically or through a trochar.

Solutions. Low sodium solutions have been used to facilitate the control of hypertension in chronic renal failure. Lipid has been added experimentally to increase the clearance of glutethimide. Albumin has been used to remove bilirubin, salicylate, and barbiturates. Sorbitol has been used in diabetic patients, and also to prevent caramelization of sugar during mass sterilization of fluid. Amino acids have been added to replace losses incurred with dialysis. Use of acetate instead of lactate has been suggested to inhibit bacterial growth and prevent peritonitis.⁵³

Recirculation dialysis was described by Shinaberger in 1965. Two catheters were inserted and fluid was circulated through a coil dialyzer. Urea clearance was as high as 100 ml. per minute, but difficulties in obtaining adequate flow rates limited the usefulness of this procedure.

Indwelling buttons. A variety of devices were used in the early 1960's to obtain repeated entry into the peritoneal cavity and avoid multiple punctures. Most of these devices were abandoned because they led to peritonitis.

Indwelling cannulas made of silicone may be implanted surgically or percutaneously and have been used successfully for over 2 years.¹⁸

The Deane prosthesis is a short Teflon tube which is inserted after the cannula is removed. The prosthesis is left in the site until the next dialysis, when it is taken out and a new cannula is inserted along the formed tract.³⁰

Simple monitoring devices, consisting of a balance, a counter weight, a mercury switch, and a buzzer, have been used to alert nurses that inflow or outflow of dialysis fluid has been completed.⁵⁹

Continuous cycling and automated production of dialysis fluid.^{37, 67} A number of such systems have been described, but they are not widely used at the present time. Hopefully they will help simplify dialysis and reduce costs.

HEMODIALYSIS

Hemodialysis is more effective than peritoneal dialysis but requires trained staff and a well organized unit. In recent years the procedure has been simplified and is now frequently done by nonmedical personnel or even by patients.

PRINCIPLES

Blood drawn from an artery is continuously circulated through a membrane dialyzer, where it is purified, and is then returned to a vein. A pump is needed to propel the blood if a high-resistance dialyzer is used. The dialyzer is immersed in a bath which contains fluid of similar electrolyte concentration as plasma. Solutes pass through a semipermeable membrane which has pores of an estimated diameter of 30 to 90 Å.⁴⁶ Transport occurs mainly by diffusion, and the concentration gradient is maintained by replenishing and circulating the dialysis fluid. Dialysis takes place only when both blood and dialyzing fluid are in motion.

The clearance concept, widely used in renal disease, is also applied to quantitate solute removal by an artificial kidney. Clearance is defined as the virtual or theoretical volume of blood completely cleared of solute per unit of time. It is expressed in milliliters per minute and must be related to the blood flow rate. The clearance of a solute depends on its molecular weight, the flow pattern through the dialyzer, and the permeability and surface area of the dialyzing membrane. Dialysance takes into account the gradient across the membrane by introducing a small correction factor for the solute concentration in the bath.⁴⁶ At a flow rate of 200 ml. per min., the dialysance of various dialyzers ranges from 70 to 150 ml. per min.^{3, 9, 13}

Water is removed mainly by ultrafiltration and only slightly by osmosis. The amount of ultrafiltration is determined by the mean hydrostatic pressure across the membrane. In practice, it depends primarily on the outflow pressure from the dialyzer and only secondarily on the blood flow rate. A pressure gradient across the membrane may be obtained by increasing the pressure in the blood compartment (positive pressure) or by applying suction on the dialysate side of the membrane (negative pressure).

DIALYZERS

Earlier dialyzers had cellophane membranes, but cuprophane is now widely used. There are two main types of dialyzers: coil dialyzers, made of sausage-like tubing, and plate dialyzers, made from sheets of membrane stacked like sandwiches. The blood flows on one side of the membrane and the dialyzing fluid on the other.

Coil dialyzers consist of long tubes of cellophane or cuprophane wound around a central core. They have a high resistance and usually require a blood pump. Non-disposable types such as the Kolff Rotating Drum (1943) and the Alwall dialyzer (1947) are mainly of historical interest. The disposable Kolff "Twin Coil" (1956)* played a great role in popularizing dialysis in most parts of the world but had an internal volume of 1200 ml. and required 2 units of blood for priming. It was later superseded by the Ultra-Flo* coil dialyzers in which the fiberglass screen membrane support was replaced by a plastic mesh. The Ultra-Flo 145 has an internal volume of 450 to 640 ml. and can be primed with saline.^{3, 9, 13} The Ultra-Flo 100 uses cuprophane instead of cellophane and has a volume of 360 to 470 ml. It is currently the most efficient dialyzer available for removal of urea and water.^{3, 9, 13}

The EX-01 Dialyzer Cartridge** represents a further advance in design. It has a volume of 180-250 ml. and is only slightly less effective than the Ultra-Flo coils. It has a single wide cuprophane channel, single arterial and venous blood lines, and fits into a neat compact Plexiglas container. It is easy to use and allows for a smooth dialysis with few side-effects.³ At the end of dialysis the blood is returned to the patient with ease. A new model, the EX-03, is only slightly larger but has greatly improved ultrafiltration capacity.

Coil dialyzers are used in a variety of "kidney machines," which consist essentially of a steel tank and a pump to circulate the dialyzing fluid. They vary in the size of the tank, the manner of preparation and distribution of the dialyzing fluid, and the number of safety devices.

In the simple tank system the bath is made up by adding dialysate concentrate to the required amount of water. The tank is emptied periodically and a new bath is made up. The most widely used model, the Kolff-Travenol* "Artificial Kidney," has a capacity of 100 liters, pumps for drainage and circulation, and a heater. It is simple, is relatively inexpensive, and requires little maintenance. Tanks as large as 300 liters, often home-made, have been used to avoid changing the bath.

Coil dialyzers may also be used in inexpensive commercially available washing machines. The washing machine agitator is removed and the coil is suspended in the tub. The drain pump is used as a circulating pump by attaching to the drain pipe a rubber hose which is connected to the coil-cannister. A lamp is used for a heater. The bath is changed

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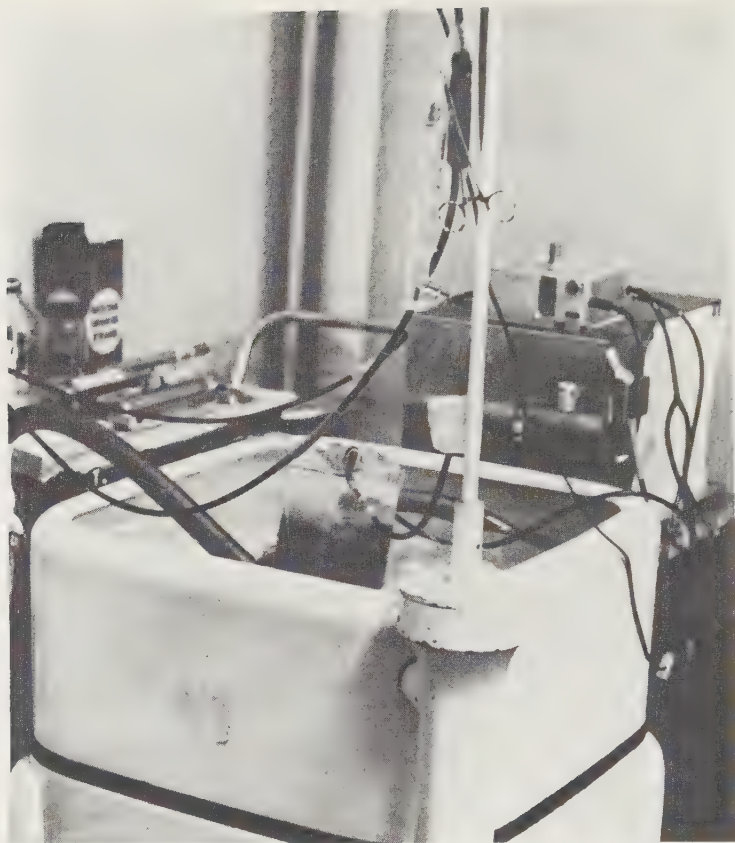


Figure 1. Hemodialysis with an inexpensive washing machine. In this system the washing machine pump is used for drainage as well as for recirculation of the dialysis fluid.

by temporarily disconnecting the rubber hose from the drain pipe. This system has been used many times when no other artificial kidney tank was available, and is effective and easy to operate.^{3, 69}

In other systems, the dialyzing fluid is stored in a separate tank and conveyed to a smaller container, where it is circulated through the coil and then discarded. A number of such systems are available. The Travenol Recirculation Single Pass (RSP)* model has a tank of 120 liters, hemoglobin and air embolus detectors, a heater, and a flow meter. It is popular but rather expensive. A less expensive version, the Travenol "Module" has recently been developed and other commercially manufactured models are also available. Many hospitals have built their own inexpensive recirculation systems. Some systems have a central tank, with dialysate delivered to bed side cannisters.

In the most sophisticated systems the tank has been eliminated and the dialyzing fluid is made up continuously from concentrate and tap

*Travenol Laboratories, Morton Grove, Illinois

water. The Milton Roy, Biosystems, Sweden Freezer, and Drake Willcock systems are widely used. Time alone will tell whether they offer any real advantages over the less complicated tank systems.

Plate type dialyzers consist of cellophane or cuprophane sheets placed between plates or boards. Blood flows between the membrane sheets while the dialysate circulates between the membrane and the plates. Several models are available. The Skeggs-Leonards dialyzer is now rarely used and has been largely superseded by the Kiil dialyzer. This has three longitudinally grooved polypropylene boards and two cuprophane compartments, all fixed together with clamps. In the Klung dialyzer, the membranes are supported on minute silicone cones. In the Miniklung dialyzer, a diamond-shaped exchange area has been incorporated to produce countercurrent flow of blood and dialysate.²⁹ Esmond's Dialung has up to 65 small plates and is effective but somewhat tedious to assemble.¹⁵

Plate dialyzers have low priming volumes and low resistance. They require no blood pump and have low running costs, but take longer to assemble. The disposable membrane envelope inserts developed by Nosé may partially solve this problem,⁴⁷ but completely disposable plate dialyzers are even more promising. One such model has been developed by Funck-Brentano in France,¹⁸ and another by Gambro in Sweden.³³

Several other types of artificial kidneys are now in the stage of clinical testing. The Capillary Kidney, developed by Stewart in 1964, consists of about 10,000 minute cellulose acetate hollow fibers with an internal diameter of 200 microns and a wall thickness of about 30 microns. It has a priming volume of about 130 ml.²² The paralld flow dialyzer of Lavender has stacked layers of cellulose dialysis tubing and a volume of less than 100 ml.³⁴ An experimental portable "wrist dialyzer," proposed by Bluemle, utilizes a pleated strip of membrane arranged in a stack and folded like an accordion. It has no membrane supports and the volume is only 40 ml.⁶

Much research has been done to produce better dialyzers. This involves development of more permeable and antithrombogenic membranes,⁶ improved membrane supports and flow patterns, better methods of dialysate circulation and distribution,⁶ use of adsorbents in the dialysis fluid, and more effective safety devices.

Many modifications of the standard technique have been devised. Patients have been dialyzed on the same Twin Coil, in the same tank, in washing machines, and in bath tubs. Sauna bath treatment may supplement fluid removal by the artificial kidney.⁶³ Calcium, sodium, or potassium concentrations in the dialyzing fluid have been varied. The use of acetate instead of bicarbonate has allowed the preparation of convenient liquid dialysate concentrates. Glucose-free and potassium-free dialyzing fluid have been used to liberalize diets and allow use of large dialysis tanks. Coils have been taken apart and rewound with new cellophane. In some units, coils are flushed and filled with saline, stored in a refrigerator, and re-used many times. There is no significant bacterial growth, and antibiotics need not be added.

ARTERIOVENOUS SHUNTS AND FISTULAS

Access to the vascular system is by a Quinton-Scribner shunt or a Brescia-Cimino internal fistula. Arteriovenous shunts are usually supplied as a single all-Silastic piece, but separate Teflon tips are also available. In most units the curved shunt has been abandoned in favor of a straight one to facilitate removal of blood clots. A stabilizing flange, as described by Ramirez, is sometimes used.

Good surgical technique is needed for long-term shunt survival. The radial artery and cephalic vein are generally used. Both vessels may be exposed by a single vertical incision, but a separate horizontal incision for the vein is sometimes preferred. Good alignment is important, and the largest tip that fits comfortably into the vessel is chosen. The shunt should be kept dry and clean but need not be dressed daily.

Average shunt life is 8 to 17 months for the arterial side and 7 to 10 months for the venous side. Complications include bleeding, extrusion, infection, and clotting. Long-term anticoagulation with small doses of warfarin sodium has been recommended to prevent clotting. Dec clotting is usually done with an Intracath catheter, but a Fogarty catheter may be needed in difficult cases. Retrograde injection of more than 2 ml. of fluid into the arterial side must be avoided because clots may be dislodged into the cerebral vessels.¹⁹ Successful use of fibrinolytic agents has been reported. Surgical revision of shunts is frequently required, and shunt angiography with dilute contrast medium may help to determine the nature and site of the defect.¹¹

Larger blood vessels such as the brachial artery or the femoral vessels⁵¹ may be used when the forearm vessels are not available. For acute or occasional dialyses, size 14 scalp vein needles or Teflon needles are sometimes satisfactory, but higher blood flow rates are obtained by percutaneous cannulation of the femoral vessels.

Difficulties with shunts have led more dialysis units to use the internal arteriovenous fistula. A 5 mm. anastomosis is made between the radial artery and the cephalic vein. The veins become arterialized and after a few weeks are distended and easily punctured. The patient is freed of having tubes in his arm but requires two venipunctures for each dialysis. Complications are infrequent, but blood flow rates are lower and a blood pump is always needed.

Forearm or leg fistulas and saphenous vein grafts have also been used. In general, fistulas have proved satisfactory alternatives to external shunts and have functioned well for several years. They have been used for home dialysis, and when inserted in the leg they may be punctured by the patient himself.⁶¹

PROCEDURE

The dialysis procedure has been simplified over the years, and methods described in books are often unnecessarily complicated. Coil dialyzers are usually used with standard equipment. The coil is placed in its cannister and connected to arterial and venous lines. The venous

bubble chamber is connected to a Tycos manometer and a Mercoid switch. The tub is filled with water at 37° C and dialysate concentrate is added. The system is primed with heparinized saline, the lines are connected to the patient, and dialysis is begun. Heparin is injected in a dose of 10 mg. per hour or as an initial dose of 50 to 100 mg., further adjustments being made according to clotting times. Regional heparinization is rarely used. Blood is pumped at a rate of 150 to 400 ml. per minute, and the outflow pressure is regulated according to how much ultrafiltration is desired. The bath is changed every 2 to 3 hours, and dialysis is continued for 6 to 8 hours. Fluid replacement may be required during dialysis to prevent excessive ultrafiltration.

The assembling of plate dialyzers is more time consuming. With the Kiil dialyzer, the membranes are sterilized in a formalin solution which must then be entirely washed away. The dialysis fluid is used in a single-pass system. As a rule, no blood pump is needed. Usual dialysis time is 10 to 14 hours. The assembly and dialysis procedure have been described and illustrated in detail.^{46, 49}

COMPLICATIONS

Technical Complications

Membrane rupture may occur because of holes in the membrane or because of sudden obstruction to outflow. Small leaks color the dialysis fluid green and cause foam to appear on the surface. When this happens, dialysis may sometimes be continued, but usually the coil must be changed. Massive rupture is rare and requires immediate stopping of the dialysis and replacement of the coil.

Clotting in the coil results from insufficient heparin administration. It may occur quite suddenly and usually starts on the venous side or in the bubble-catcher. In most cases the coil must be replaced.

Improperly prepared dialyzing fluid may occur because of human error or because of failure of automatic equipment. Pain in the area of the shunt may be an early indication that the dialysate is hypotonic.

Leakage from connections is avoided by tightening and taping all connections.

Poor arterial supply may be due to spasm, small arterial bore, kinking of lines, or sucking of intima into the cannula lumen. It is recognized by collapse of the arterial line. The pump should be slowed, because air may be sucked in by negative pressure and cause embolism.

Venous obstruction may result from kinking, spasm, or clotting. It increases the outflow pressure from the dialyzer and, if uncorrected, causes membrane rupture.

Dialyzer distention was frequently seen with the earlier, larger dialyzers. If the coil was primed under low pressure it would become distended with blood at the beginning of dialysis and cause hypotension.

Medical Complications

Malaise, vomiting, cramps, and headaches were frequently seen with earlier dialyzers, but the occurrence of these symptoms has become less common.

Hypotension is usually due to excessive ultrafiltration, but may be due to bleeding or other medical problems.

Hypertension is usually a manifestation of the underlying disease but may be aggravated by fluid or blood administration. It sometimes follows excessive ultrafiltration, perhaps because of renin production.

The dysequilibrium syndrome, characterized by drowsiness, confusion, headache, vomiting, or convulsion, occurs when the biochemical abnormalities of uremia are corrected too rapidly. It is believed to be due to cerebral edema caused by too rapid reduction of the urea level in the extracellular space.⁵⁶ This complication may be prevented by avoiding prolonged dialysis in severely uremic patients, and perhaps by adding extra glucose to the dialysis fluid.

Convulsions may be due to hypertension, electrolyte imbalance, acidosis, or anoxia.

Arrhythmias may be associated with underlying heart disease, electrolyte imbalance or digitalis intoxication. Pseudoarrhythmias are artefactual electrocardiographic changes caused by pulsations of the blood pump.³⁹

Hematological effects such as significant hemolysis and thrombocytopenia are uncommon, but platelets may be destroyed at very high flow rates. Profound neutropenia has been observed within 2 to 15 minutes after the start of dialysis but produced no untoward effects.³¹ Transfusion reactions may be due to pyrogens, allergy, or incompatible blood.

Infection of shunts may lead to severe septicemia and septic embolization. Growth of organisms in the circulating pump may allow diffusion of toxins across the membrane and cause pyrogenic reactions. Infection with unusual organisms such as *Bacillus cereus* has occurred with the Kiil dialyzer.

Anticoagulation rebound with severe bleeding has been described after regional heparinization, perhaps owing to late dissociation of heparin-protamine complexes or (less likely) re-entry of heparin into the circulation from the lymphatics.²⁶

Hyperglycemia, with agitation, confusion, disorientation, and fatal cardiac arrest, has occurred in a patient who was dialyzed against a glucose concentration of 7000 mg. per 100 ml. The serum sodium level remained normal and there was no ketosis or acidosis, but the blood sugar was 3400 mg. per 100 ml. and the plasma osmolarity was 487 mEq. per liter.⁵⁰ Reactive hypoglycemia following use of hypertonic dialysis fluid has also been reported.⁵⁴

Acidosis may be caused by contamination of dialysis tanks during prolonged dialysis for drug intoxication. It has been attributed to the production of organic acids by bacterial metabolism, and may produce neurological changes, hypotension, and arrhythmias.⁵⁷

Hard water syndrome has been described following the use of a faulty water softener. Patients were dialyzed against a calcium concentration of 14.8 mg. per 100 ml. and developed serum calcium levels of 14 to 20 mg. per 100 ml. Symptoms were vomiting, extreme weakness, atypical changes in blood pressure, burning of the skin, and a tendency to clotting in the arteriovenous shunt.¹⁶

Magnesium intoxication has occurred in patients who were accidentally dialyzed against a dialysis fluid magnesium concentration of 15 mEq. per liter. They had blurred vision, flushing of the face, hyperreflexia, and inability to stand because of ataxia. Some had hypotension.²³

Copper intoxication may occur following use of a faulty deionizing column.¹⁰ Symptoms include weakness, dizziness, vomiting, abdominal pain, diarrhea, intravascular hemolysis, hypotension, coma, and occasionally death.

INDICATIONS

Acute renal failure may require treatment by dialysis. Nevertheless, it is difficult to lay down absolute indications for dialysis in acute renal failure because every case must be judged individually. It is better to dialyze too early rather than too late, and prevent rather than treat the symptoms of uremia. Arbitrary laboratory values have frequently been cited, but the appearance of the patient and his clinical condition are often better guides.

Both hemodialysis and peritoneal dialysis are satisfactory ways of treating acute renal failure. Many hospitals treat routine cases by peritoneal dialysis, but hemodialysis is preferred in patients with extreme obesity, multiple adhesions, abdominal trauma or surgery, aortic aneurysm, or suprapubic cystostomy. Early and frequent hemodialysis is the treatment of choice for the severely ill hypercatabolic patient with multiple injuries, infection, or intra-abdominal problems; the prognosis is often grave and death is usually caused by the underlying disease, but earlier referral and vigorous dialysis may reduce mortality.

Preparative dialysis. This term was coined by Barry to indicate the use of dialysis to prepare patients for stressful situations such as transport to other centers, diagnostic procedures, or surgery.² The prognosis for such patients is improved if they are treated by dialysis before undergoing these procedures.

Renal failure of unknown etiology. When a patient is seen for the first time, it is often difficult to tell if he has acute or chronic renal failure. Dialysis is often done on an emergency basis, and must be continued until a definitive diagnosis is made or until it has been shown that no renal reserve is left.

Exacerbations of chronic renal failure. Patients with stable renal function may develop severe uremia because of dehydration, infection, bleeding, or worsening of their disease process. Sometimes they can be treated conservatively, but often it is safer and more expedient to consider a limited number of dialyses in the hope that they will return to their previous level of renal function.

Intermittent or periodic dialysis. Some patients with chronic renal failure are unable to maintain life unaided but have some residual renal function and can be managed successfully by an occasional dialysis. This is most successful in patients with polycystic disease and various renal medullary syndromes. A daily urine volume of at least 500 ml. is required.

Anuric and severely hypertensive patients are unsuited for intermittent treatment, and require regular dialysis.

Miscellaneous. Hemodialysis has also been used to treat drug intoxication, electrolyte imbalance, hypercalcemia, intractable heart failure, gout, and, less profitably, hepatic coma and porphyria.

MAINTENANCE DIALYSIS

Maintenance dialysis is begun when a conservative regimen, supplemented by occasional dialyses, becomes inadequate to maintain life or avert the onset of serious complications. The decision to initiate regular dialysis is based on clinical and biochemical criteria. Unnecessary delay should be avoided, because the complications of uremia may be difficult to reverse. The clinical appearance of the patient, the rate of rise in the blood urea nitrogen, and the daily urinary volume are the most important criteria used in making this decision.

Patients considered for maintenance dialysis must be evaluated from medical, social, and psychiatric points of view. The ideal comprehensive approach would permit smooth transition from the conservative phase of therapy to dialysis, with early emphasis on training for treatment in the home.

CRITERIA FOR SELECTION

As long as facilities for dialysis remain limited, some means of selecting patients is needed. Decisions are usually made by a committee which consists of medical and sometimes lay people. General guidelines have been laid down but should be applied with flexibility, because it is difficult to predict how well individual patients will do on the program. Some of the criteria used are as follows.

Age is an important consideration, because best results are obtained in patients between the ages of 18 and 45 years. Dialysis is more difficult in children, and patients over the age of 50 have higher morbidity and mortality rates.

Body size and urine volume. Large patients produce more breakdown products and need longer periods of dialysis. Patients who have some residual urine output may require less dialysis. These factors may become important when dialysis facilities are very limited.

General condition, complications, and associated diseases. Rehabilitation may be virtually impossible in patients in whom dialysis was delayed too long. Wasting may be extreme. Patients with severe neuropathy or bone disease may not be able to walk again. Patients with severe degenerative vascular disease are higher risks and may be unsuitable for transplantation. Even more problematic are patients with systemic illnesses such as brittle diabetes, collagen diseases, or neoplasia.

Social and psychiatric factors are most important in determining the success of a maintenance dialysis program. The demoralizing effect of unstable, uncooperative, and querulous individuals on other patients and on the nursing and technical staff cannot be overestimated.

Poor vessels for arteriovenous shunts constitute an indication for peritoneal dialysis or early transplantation.

Irreversible acute renal failure. Patients who fail to recover from acute renal failure would seem to be especially suitable for chronic dialysis because they usually have no systemic disease and have not suffered from a long, debilitating illness.

Suitability for transplantation is a consideration in units set up only to maintain patients for renal transplantation.

PROGRAMS

The first maintenance dialysis program was begun in 1960. Since then, dialysis has been done in hospitals, satellite centers, motels, church basements, doctors' offices, homes, and even trailers. The cost has varied from \$3,000 to \$20,000 per year and has been borne by patients, insurance companies and government institutions.

Patients are usually treated two or three times weekly, for 6 to 8 hours with coil dialyzers or for 10 to 14 hours with plate dialyzers. Dialysis units vary in size from 2 to 20 beds and may treat from 1 to 100 patients. Dialysis is done by nurses or technicians, and physicians are generally not in constant attendance. Some hospitals run two shifts per 24 hours. Night dialysis enables patients to work during the day.

In the United States, approximately 1000 patients are being dialyzed in the home to reduce costs and relieve pressure on intramural facilities. Training is usually undertaken in the hospital but may also be initiated in the home. Either coil or plate dialyzers may be used, and patients arrange their own dialysis schedule. Shaldon has recommended unattended self-dialysis during the night, using an arteriovenous internal fistula.⁶⁰ This is economical, avoids dependency on relatives, and allows the patient to work, but requires failure-proof safety devices.

Patients on maintenance dialysis should take a high caloric diet of about 2000 to 3000 calories supplied mainly as fat and carbohydrate. Special supplements may be required to achieve this. Most programs allow 30 to 50 grams of protein per day, but emphasis should be on adequate nutrition rather than on restriction. Fluid intake is generally limited, to allow a weight gain of no more than 1 lb. per day. Hypertension should be treated by water and salt restriction, supplemented by antihypertensive drugs if necessary. Vitamin supplements are usually prescribed. The emphasis is on rehabilitation and return to work. Many patients lead relatively normal lives. They are able to withstand many stresses and have major surgery.²⁵ There is however an annual mortality rate of 10 to 30 per cent, and the 3 year survival rate is approximately 70 per cent.

COMPLICATIONS

Complications may result from dialysis itself, from inadequate dialysis, or from a continuation of the uremic process.

General symptoms such as malaise, fatigue, insomnia, weight loss, and failure to thrive or muscular wasting may be due to inadequate dialysis, malnutrition, shunt infection, or psychological problems. Some patients do poorly on dialysis and should be considered for transplantation.

Psychological symptoms include anxiety, depression, feelings of dependency, schizophrenic reactions, or psychotic reactions.¹⁰ Patients may handle their stressful situation by denial, sublimation, or projection. Problems of ambivalence among the medical staff have also been described.¹²

Itching is difficult to treat and antipruritic agents are rarely helpful. Hot baths may be tried. Itching is only partially helped by prolonging dialysis time, but may disappear after parathyroidectomy.

Hepatitis has occurred sporadically or in epidemics and has affected patients and staff. Infectious and serum hepatitis may occur. Patients tend to have a milder disease than staff, and may have prolonged elevation of serum transaminase levels and persistence of Australia antigen.³⁶ Prevention of hepatitis includes use of frozen blood, reduction in transfusions, rigid hygiene in the dialysis room, and use of proper disinfectants. Sodium hypochlorite has been highly recommended. Gamma globulin injection may be used when hepatitis occurs throughout a unit.

Pericarditis, a well-recognized complication of uremia, may sometimes appear after many months of apparently successful dialysis. The relation to heparin is unclear. Some patients will improve with increased dialysis time, but sometimes a pericardial friction rub will not subside until after a successful renal transplant has been accomplished. Cardiac tamponade is treated by pericardial aspiration, but in some cases a pleuropericardial window must be established. Subacute constrictive pericarditis has also been reported, and some patients have fibrinous pleuritis.⁴³

Anemia is normochromic normocytic and is due to decreased production of renal erythropoietin and to a defect in red cell iron incorporation. A component of hemolysis or bleeding may also be present. Megaloblastic erythropoiesis is very rare, and most patients have normal red cell folate levels and no overt folic acid deficiency.³⁸ Vitamin B₁₂ levels are also normal. Iron deficiency is uncommon. In recent years, most units have reported a reduction in blood transfusion requirements, and some use almost no blood transfusions at all. It is now usual to withhold blood until the hematocrit drops to 18 or even 12 per cent, or even to transfuse only when patients become symptomatic. In general, patients tolerate low hematocrit levels very well. Moreover, it has been shown that blood transfusions depress bone marrow activity and endogenous erythropoietin production.

Hypertension is a serious problem in many patients. Some patients may be treated by rigid salt and water restriction supplemented with small doses of antihypertensive drugs. Others respond poorly to such conservative therapy and constantly fluctuate between severe hypertension and disturbing postural hypotension. They lose weight, fail to thrive, and may require bilateral nephrectomy as a final resort. Many of these patients have high plasma renin levels.⁷⁰

Uremic osteodystrophy represents a complex of osteomalacia, osteitis fibrosa, and osteosclerosis.³² Apparently it is caused mainly by secondary hyperparathyroidism and an acquired resistance to vitamin D. A defect in the metabolism of 25-hydroxycholecalciferol, the active constituent of vitamin D, has been described. Diagnosis is difficult because bone pain may be absent, the alkaline phosphatase and radiological studies normal, and the bone biopsy examination unrepresentative. Methods of prevention and therapy are poorly understood. There is no evidence that bone lesions may be prevented by prolonging dialysis time. Most units use a dialysate calcium concentration of 6 mg. per 100 ml. and administer aluminum hydroxide when the calcium phosphate product exceeds 75 mg per 100 ml. Vitamin D may be used for predominant osteomalacia but carries with it the danger of metastatic calcification. Parathyroidectomy is indicated in the face of unequivocal osteitis fibrosa. Patients may also have osteoporosis due to protein malnutrition and perhaps prolonged use of heparin. The role of fluoride is unclear.

Metastatic calcification may occur in patients who have an unduly high calcium phosphorus solubility product. Berlyne has described a "red eyes syndrome" caused by deposition of crystals in the cornea and conjunctiva. Pseudo-gout arthritis may be associated with calcium apatite crystals in the synovia. It responds to colchicine and may improve when the serum phosphate level is lowered with aluminum hydroxide.⁴² True gout may also occur. It responds to colchicine and to treatment with allopurinol, a drug which is well dialyzed.

Peripheral neuropathy is of a sensory-motor type and typically affects the lower extremities. It usually occurs in patients who were allowed to remain uremic too long before dialysis was begun. Occasionally it manifests in the very early stages of dialysis with a relatively abrupt onset. In contrast to uremic bone disease, it is less likely to appear late in the course of an adequate maintenance dialysis program. Improvement in nerve conduction and some symptomatic benefit is usually obtained by prolonging dialysis time, but the greatest improvement is observed after renal transplantation. Relief has also been reported after bilateral nephrectomy.

A "burning feet syndrome" may also be observed in patients on maintenance dialysis and may not necessarily be related to peripheral neuropathy.

Strokes occur more commonly than is generally appreciated and are the result of underlying vascular disease and hypertension. Embolic phenomena have also been described and may be caused by intra-arterial fluid injection used to declot shunts.¹⁹

Subdural hematomas were recently reported in 3 patients.⁴² Diagnosis may be difficult, because the clinical features resemble hemodialysis dysequilibrium.

Heart failure accounts for one third of the deaths in Europe but seems to be less common in America. It is usually due to hypertension and overhydration, but may be due to underlying heart disease. A specific cardiomyopathy, perhaps caused by a toxic uremic product, has also been described.

Bacterial endocarditis with aortic incompetence due to organisms of probable mouth origin (*Streptococcus viridans* and *Streptococcus D*) has been reported in two patients, one of whom had a Teflon Silastic shunt, and the other an internal fistula.²⁰ Diagnosis in the presence of chronic renal failure may be difficult and delayed.

Recurrent septic pulmonary emboli have occurred from infected arteriovenous shunts. There is usually evidence of local inflammation as well as radiological findings in the chest films.²¹

Hemosiderosis was frequently observed in the earlier days of chronic dialysis but has become less frequent with the reduction in blood transfusion requirements.

Gastrointestinal bleeding may be caused by uremia, heparin, oral anticoagulants, or stress ulcers. Some patients with duodenal ulcers have required surgery.⁷

Gynecomastia may be unilateral or bilateral. The pathogenesis is unknown but may resemble the refeeding gynecomastia of malnutrition.¹⁷

Loss of libido, impotence, and sterility are common but not invariable. Several notable exceptions have been reported.¹⁴

A bleeding tendency is believed to be caused by a qualitative platelet defect and is partially corrected by dialysis.⁶⁴ Difficulties may arise during shunt surgery, bilateral nephrectomy, or kidney transplantation.

Hyperkalemia is rarely a problem in well-dialyzed patients, but may create difficulties during cadaver transplantation surgery. Fresh blood, preferably pretreated with potassium exchange resin columns, should be used in this situation.

Carbohydrate intolerance may be manifested by an abnormal glucose tolerance curve, but it is not a clinical problem.²⁷ It is believed to be due to the accumulation of a substance of small molecular weight which antagonizes the effect of insulin.

CONCLUSION

Only a decade ago, patients with end-stage renal failure were doomed to certain death. As we enter the 1970's, uremia is no longer an always fatal disease. The lives of many patients have been extended successfully, and the first patient treated by maintenance dialysis is still alive after 10 years. More than 3500 patients are currently being treated in the United States, and of these, almost one third are dialyzed in the home. Yet these numbers fall short of the need, and existing facilities must be expanded. Further progress is necessary to reduce the mortality rate and to improve the quality of life of dialyzed patients. The object of maintenance dialysis is complete rehabilitation and return to a normal and productive life. If this is not achieved, we shall be like those physicians whom Plato describes in the third book of the Republic as draining off a little here, pouring in a little there, giving man a long and miserable life, and making death a long process. We must do better.

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Psychiatric Observations in a Chronic Hemodialysis Program

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There have been a number of reports of psychological stresses associated with chronic hemodialysis. From these, it is evident that centers vary in terms of the kind of emotional adjustments their patients make. Sand et al. reported that only 2 of their 23 patients made a poor adjustment to dialysis; Johnson et al.⁸ said, "In general, these patients made a remarkably good adjustment to this restrictive and stressful mode of existence." On the other hand, Shea et al.¹⁹ observed 2 schizophrenic-like episodes, 1 psychotic depression, and a number of severe neurotic depressive reactions in their series of 9 patients. Irritability, intense dependency, and insatiable demands were characteristic of many of their patients. Retan and Lewis¹³ reported suicidal thoughts and other symptoms of depression, and poor cooperation in shunt care and dietary programs.

The chronic hemodialysis unit at Presbyterian-St. Luke's Hospital is a 4 bed unit which treats 12 patients. Our hospital has a kidney transplant program, and patients are accepted for both dialysis and transplantation. Patients are usually dialyzed three times weekly for a period of 6 hours.

The following observations are based on the author's work as the psychiatric consultant to the program during the past 2 years.

SELECTION OF PATIENTS

All patients accepted into our program are evaluated prior to acceptance by a team of physicians, a nephrologist, a urologist, a transplant surgeon, and a psychiatrist (the author). The nephrologist tells the patients that they will be evaluated by the several specialists listed. If a patient raises a question about the need to see a psychiatrist, he is told that this is a routine part of our evaluation of renal patients.

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Psychiatric interviews with renal patients who are relatively normal from a psychological standpoint are a challenge to a psychiatrist. The author may explain that some patients with kidney trouble become nervous, depressed, or develop other symptoms. Interviews must be handled in a sensitive way. One cannot be timid; certain questions are necessary for the process of selection and to give us data which will be helpful in managing the patient if he is accepted into the program. On the other hand, some people are reluctant to talk about private thoughts and feelings unless they are having psychiatric problems and want help with these. The patient's wish for privacy in certain areas not important in terms of dialysis is respected, and unnecessary discussion of painful feelings and memories is avoided.

Patients are usually seen for two 30 minute psychiatric interviews. In the first interview, rapport is established and relatively neutral historical data are obtained. In the second interview the patient is usually more open and is willing to talk about some of his thoughts and feelings about the illness, as well as dialysis and transplantation. The standard psychiatric history is modified to emphasize areas important to dialysis and transplantation. The past medical history is explored in terms of the patient's emotional reaction to previous medical and surgical problems. Information is obtained about the patient's cooperation with conservative medical management of his renal disease. The nature of relationships with family and friends is discussed to determine the amount of emotional support the patient will receive if he is accepted into the program. A vocational history is obtained, and recreational interests are noted. Some information is obtained about relationships with parents and psychological development during childhood. This helps us to understand regressive phenomena which emerge during treatment with the artificial kidney. Strengths and the capacity to adapt to stress are noted, as well as weaknesses and psychopathology.

We attempt to evaluate patients relatively early in the course of uremia, before the organic brain syndrome which accompanies renal failure interferes with the psychiatric assessment; however, this is not always possible. The psychiatrist must be alert not to confuse psychiatric signs of uremia with problems of psychogenic origin; on the other hand, as with other organic brain syndromes, the clinical picture of uremia reflects an interaction of organic and psychological factors. Anxiety, the content of hallucinations, and so forth are determined by past psychological development, current conflicts, and individual patterns of defense and coping. Apathy, drowsiness, and inability to concentrate for long periods of time are early signs of uremia. As uremia progresses, speech may become slow and slurred, and memory may become erratic. Irritability and restlessness may be seen, and insomnia can be a problem. Muscle twitching sometimes occurs, and muscle spasms can be particularly troublesome to the patient in the twilight period just before going to sleep. Patients tend to become defensive and often paranoid. At times, psychotic symptoms such as delusions and hallucinations are seen.¹⁰ One of our patients developed the delusion that we were trying to kill her. Eventually the patient becomes comatose.

If a patient is severely uremic, it may be necessary to treat him with peritoneal dialysis before an adequate psychiatric evaluation is possible. In some cases, there is a lag between the correction of the chemical signs of uremia and clearing of the organic brain syndrome. Schreiner¹⁶ has observed patients whose sensorium cleared as long as 6 to 8 days after dialysis at a time when their blood urea nitrogen had risen to a higher level than that preceding dialysis.

Sand et al.¹⁵ found a small but consistent tendency for more intelligent patients to be more cooperative and to make a better emotional adjustment to dialysis. Patients in their group who made a poorer adjustment tended to be defensive and to deny even normal amounts of anxiety and difficulty in adjusting. Patients making a better adjustment showed less of a tendency to use somatic defenses such as hypochondriasis. Retan and Lewis,¹³ who accepted patients on a "first come, first served" basis, described a superficially cheerful patient who turned out to be covering up a severe depression with a manic façade. He became violent and abusive at home and threatened the safety of his grandchildren. His shunt became disconnected in public places on six occasions, despite meticulous care given to protective dressings. The sixth episode led to his death and occurred under circumstances that strongly suggested suicide.

Schupak et al.¹⁷ selected patients on the basis of four criteria: (1) eligibility for hospitalization in a municipal hospital in New York City, (2) availability of an opening in the chronic dialysis program, (3) absence of disabling disease other than one of renal origin, and (4) an indication that the patient was likely to cooperate in his own care. They found some correlation between survival and intelligence as measured by the Wechsler Adult Intelligence Scale, the mean I.Q. for patients still under treatment being 95.0, as compared with a mean value of 84.4 in those who had died; however, they also noted that certain patients with low intelligence did well in the program and were successfully rehabilitated. They also found a correlation between the length of cannula survival and I.Q. Mean cannula survival for both artery and vein was 5.6 months for those with an I.Q. greater than 100, as compared with 4.3 and 4.0 months for those with an I.Q. below 100.

Schupak et al. treated five teenagers in their program. One died as a result of her inability to cooperate. Another experienced great difficulty in adhering to her diet and caring for her shunt; as a result, she required frequent hospitalizations. The importance of strong support from an understanding, intelligent, and cooperative family in teenage patients was noted.

Abram² believes that patients should be rejected only on medical (including psychiatric) grounds. He stated that the only psychiatric contraindications are psychosis (unrelated to uremia), in which impaired reality testing makes the patient unable to adapt to dialysis, and mental retardation, which prevents the patient from understanding what is required of him in terms of shunt care, diet, and so forth. We do not accept patients for our program whose low intelligence or whose psychiatric problems (such as a psychosis or excessive rebelliousness) are likely to prevent satisfactory cooperation with the dialysis regimen.

STRESSES OF DIALYSIS

Once a patient is accepted for dialysis, there is a danger that he will simply exist rather than live. To be as active and productive as his disease permits and to get some happiness out of life, he must adapt to a number of stresses. Some of these stresses are similar to those other chronically ill patients must face; others are unique to the dialysis situation.

The medical status of the dialysis patient is fragile and unpredictable from week to week and even from day to day. Patients cannot predict when they will feel reasonably well and when they will feel sick, and they do not know when a new medical problem will occur. This is particularly difficult for patients whose jobs require that they function at a consistently high level. Impotence and loss of sexual desire are common problems. External shunts are a frequent cause of anxiety. Patients do not know when infection or clotting will occur, and the shunt is a constant reminder of their precarious status. Patients also worry that they will run out of shunt sites. Female patients may be bothered by changes in their appearance such as discoloration of their skin. Dependence-independence conflicts can be aroused by dialysis.¹ Some patients find it difficult to be dependent on the artificial kidney during dialysis and function independently at other times. It is tempting to depend too much on family members when not on the machine.

Wright et al.²¹ divided the psychological stresses of dialysis into three groups. First, there are actual or threatened losses. There are losses of body function due to weakness and due to complications in multiple organ systems. Jobs may be lost, and those of our patients who are working report a decrease in productivity. Medical bills lead to a loss of financial security. The second group of stresses relate to injury or the threat of injury. Multiple surgical procedures are sometimes necessary to revise external shunts and change their locations. If internal shunts are used, patients have to look forward to being stuck with a large-bore needle at the start of each dialysis. The third group of stresses relate to frustration of instinctual drives. Dietary restrictions lead to a loss of the gratifications that accompany eating. Male patients in particular have limitations placed on normal outlets for the aggressive drive. They cannot compete as successfully at work, and their capacity to participate in athletics and other physical activities is limited. This can be a particular problem with patients who have been oriented toward physical rather than intellectual activities.

Beard⁴ discussed the fear of death and the fear of life in dialysis patients. Beard's patients became afraid of dying when they learned about the seriousness of their renal disease. In most of the cases the next reaction was denial of the fear by denying that they had a serious disease. Following the period of denial, feelings of discouragement, sadness, and hopelessness appeared. At times all of the patients felt the crushing load of the fear of the imminent death. Some of them admitted feelings of resentment and envy of others who had not suffered the loss of good health. The fear of living an unsatisfactory life as a chronically ill and handicapped person seemed almost as intolerable as the fear of immi-

nent death to the patients in Beard's series. It is of interest that the patients who made the best adjustment to their disease and the uncertainty of their future were those who had the best ability to relate to other people and who had a close relationship with someone to whom they could turn at times of stress and discouragement.

Organic Brain Syndrome

Several of our patients have reported symptoms of an organic brain syndrome either during or shortly following dialysis. E. C., a 24 year old owner of a decorating business, felt "vague" after dialysis. His memory was not as good as usual; he would start talking about something and forget what he was going to say. On the way home he confused traffic lights with automobile headlights. J. R., a 32 year old carpenter's helper, asked to see the author during dialysis because he was "mixing up what was real and what was unreal." Mr. R. had a puzzled look on his face as he talked about his problem. He said, "I could be the King of Egypt or an emperor in the past. I could be somewhere else, another country. I am both bigger and smaller. I can do anything I want to do." Mr. R. recognized that what he was saying was irrational, and he did not show the disturbed emotions that one would see in a functional psychosis. Parenthetically, the grandiose content of Mr. R.'s thoughts probably reflected his sense of being weak and impotent because of a combination of renal disease and severe pulmonary disease secondary to uremia.

De-Nour et al.⁶ gave psychological tests to their patients during dialysis and found defects in intellectual functioning. Wakim²³ and Tyler²² described a disequilibrium syndrome in connection with dialysis. The syndrome includes restlessness, headache, nausea, an elevation in blood pressure, twitching, and on occasion, convulsions or coma. Ventricular tachycardia, cardiac irregularities, and cardiac arrest can also be seen. Tyler noted that the electroencephalogram deteriorated during the course of dialysis and returned to its pre-dialysis level or improved during the next 1 to 3 days. These changes were most characteristic of long runs on the artificial kidney or rapid and extreme adjustments of either urea level or acidosis. On occasion, for unexplained reasons, these phenomena were delayed 8 to 24 hours after the run. It was not unusual in Tyler's series for dialysis to change serum chemistries to normal or nearly normal levels while the patients got worse clinically. The patient then improved on the second and third day after dialysis, despite deteriorating chemical values. Kennedy¹¹ studied uremic patients during hemodialysis by means of continuous encephalographic recordings. Either the encephalogram became abnormal during dialysis, or abnormalities present at the beginning of dialysis became more severe. Hampers et al.⁶ found deterioration on the encephalogram following dialysis in some of their patients. A repeat tracing 20 to 24 hours after the end of dialysis showed either a return of the recording to its pre-dialysis quality or an improvement over the pre-dialysis tracing.

Anger

De-Nour et al.⁶ believe that the dependency connected with being a dialysis patient creates aggressive feelings which cannot be expressed.

They point out that these patients are dependent for life itself on the machines, on the staff who treats them, and on the society that pays for the treatment that they themselves cannot afford. De-Nour et al. believe that defenses are mobilized against aggression. However, these defenses tend to be brittle, and relatively small stresses can lead to anxiety, depression, or paranoid behavior.

We believe that anger is an important affect in dialysis patients. These patients are confronted by a number of anger-provoking situations. At best there are limitations on their functioning. They often have serious financial problems and insecurity with respect to jobs. Complications in multiple organ systems occur despite good medical care, and some pain and discomfort is inevitable. Sometimes pain is inflicted by staff members who are working with shunts, despite skillful technique and a gentle approach. The dialysis process sometimes produces nausea, headaches, and other symptoms. Sick people often put up with such discomforts without complaint. They recognize that they are being helped, and they can see an end to the pain and discomfort when they recover from the illness. The dialysis patient, however, repeatedly faces anger-provoking situations over a long period of time. If a living donor is not available, he can look forward to a kidney transplant only as something that will happen at some indefinite time in the future.

Yet, it is difficult for patients to be angry at a miraculous process that saves their life three times a week, week after week. It is difficult for them to be angry with the kind and conscientious physicians and technicians who operate the machines and take care of them, even when they cause pain. And if patients are tempted to be angry, there may be a fear, either conscious or unconscious, of retaliation. Sonnenberg and Kaplan²¹ report the feelings of a patient whose rejected kidney transplant had to be removed. She felt that she had failed her surgeon. In response to this, she feared that he would take her off the artificial kidney and abandon her. MacNamara¹² quotes one of her patients on dialysis: "If you tell them [the staff] to go to hell, they can kick you out of the hospital." Usually, when a patient becomes angry with his physician or dissatisfied with his care, whether the anger and dissatisfaction are justified or not, it is relatively easy for him to change doctors. It is not as simple to find another dialysis program.

We believe that it is important for our patients to feel relatively free to express their angry feelings about the pain, discomforts, and frustrations connected with dialysis. At times, this freedom makes staff members uncomfortable, but it is therapeutic for patients in terms of reducing the level of emotional tension. If the anger is not expressed directly, there is a danger that it will be directed inward and lead to depression, will be projected to other people and lead to paranoid symptoms, or will be displaced to family members and complicate already problematic family situations. J. R. had a low threshold for pain. He had a shunt revision under local anesthesia. He experienced pain and felt that the surgeons were insensitive because they continued with the procedure. He was furious after the operation. He was encouraged to express his anger to the author. He ranted about the surgeons for 15 minutes and talked about wanting to punch the attending surgeon. Mr. R. felt better

after this outburst and presented no problems postoperatively in terms of pain medication.

Suicidal Behavior

Abram³ investigated suicidal behavior in chronic dialysis patients at 201 centers. Of a total of 3,478 patients, 192 exhibited life-threatening behavior. Twenty successfully committed suicide, 17 unsuccessfully attempted suicide, 117 died from inability or unwillingness to follow the medical regimen, 9 died because of accidents such as shunts coming apart, and 29 withdrew from the programs.

The risk of suicide should be assessed in dialysis patients who develop severe or moderately severe depressions. Some patients will volunteer thoughts about killing themselves; others must be asked. It should be added that one need not be a psychiatrist to question patients about self-destructive thoughts. Patients are not offended if they are tactfully asked such questions as: "Do you sometimes think about ending it all?" and "How close have you come to acting on these thoughts?"

Several patients in our program have talked about killing themselves; however, there have been no suicide attempts. J. C., a 42 year old foreman, was somewhat depressed and hostile when he was accepted for dialysis. He was a hard-working, upward-striving man who was impatient with delays. He looked forward to a nephrectomy as a prelude to receiving a kidney transplant. When the nephrectomy was postponed, Mr. C. threatened to jump out of a window. He did become more depressed because of the delay, but there was an element of manipulation in his threat, as well. His depression lifted after the nephrectomy.

R. B. was a 33 year old manager of a furniture department in a department store. He was fired when he developed renal failure, and it was difficult for him to find another job because of his physical problems. He opened up a cleaning and laundry business, but was too weak to run it. Mr. B. had a myocardial infarct, and he had angina on exertion. Mr. B. said in a matter-of-fact way that he sometimes thought of taking an overdose of sleeping pills; however, he did not act on this thought.

We take the position that it is natural for dialysis patients to consider killing themselves, and we encourage them to express themselves freely about their depressive feelings. However, we also take the position that each of our patients has something to live for.

Denial

We have observed denial in some of our patients when they are told they have a fatal illness and will die unless they have repeated treatments with the artificial kidney. We have found that physicians may have to repeatedly explain things they think the patient already understands; some patients can only accept the information they are receiving about renal failure, dialysis, and transplantation in small doses.

Denial of certain aspects of reality or denial of feelings about these unpleasant things is also seen in the course of dialysis. It is not surprising that dialysis patients use this defense mechanism. Not only do they have end-stage renal disease, but in time they may have an overwhelming collection of medical problems: infections, hypertension,

peripheral neuropathy, anemia, secondary hyperparathyroidism, and so forth. At times denial may protect patients from emotional decompensation. We have a flexible attitude toward denial in our program. If patients experience feelings of anxiety, depression, or anger, this is accepted, and they have regular opportunities to express these feelings when they are seen for follow-up interviews. On the other hand, if patients use denial, this is respected. Denial could prevent a patient from seeking prompt attention for medical complications. Such a situation would be an indication for encouraging patients to talk about painful thoughts and feelings even though they preferred not to do so; however, we have not encountered this problem in our program. Our patients have not employed denial in such a way that their medical care has suffered.

Transplantation

Patients are accepted into our program for both chronic hemodialysis and transplantation, and all of our patients look forward to the day when they will receive a new kidney. While this contributes to a hopeful attitude, there is a danger that patients will simply exist, deferring rehabilitation until they receive a transplant. Since many of them must wait long periods of time before a kidney becomes available, this is undesirable. The staff does not discourage patients from thinking about transplantation, and the staff also looks forward to transplantation, particularly for patients who are doing poorly on dialysis. However, we encourage patients to lead lives that are as active and as full as their physical condition permits while they are being treated with the artificial kidney.

Phases in Adaptation

Abram² described several phases in a patient's adaptation to dialysis. Before the first treatment, the patient shows central nervous system manifestations of uremia: fatigue, apathy, drowsiness, difficulty concentrating, depression, and instability. Delirium may be seen. During the first to third weeks of dialysis, there is a shift to physiological equilibrium. During this phase apathy lessens. The patient reacts with euphoria as he realizes that he has been given a reprieve. Anxiety is also seen during this period. By the third to fourth week (6 to 8 dialyses), the patient has reached a state of equilibrium and faces the reality of his situation. He is physically weak and bothered by symptoms such as headaches and vomiting. Depression often appears as the problems of living with dialysis becomes apparent. It requires about 2 months before the patient reaches the point physically and psychologically where he can return to work. One cannot force the patient back to work prematurely, and psychotherapy may be necessary to help him deal with his depression and conflicts about dependence versus independence. It may take a patient 6 months to a year to reach a level of satisfactory adaptation to the rigors of dialysis. Abram also observed "anniversary reactions," with an increase in anxiety around the end of the first year of dialysis.

Psychiatric Complications in Children

Children treated with chronic hemodialysis can present special problems in terms of psychiatric complications. Salisbury¹⁴ reported the behavioral responses of a 9 year old girl who was treated with dialysis for 9 months before transplantation. Prior to her illness, the child had been a superior student in school. She had been extremely independent and had been a leader of other children. As the months passed, marked change was noted in her behavior. She became very passive and was content to let staff members do everything for her. Her interests narrowed, and her chief interest became food. Her schoolwork deteriorated, and it became difficult for her to concentrate. She drank water from the tap in the washroom, and self-destructive behavior appeared. She picked her nose until it bled. She picked at her shunt and threatened to pull out the tubes.

Our experience with children is limited to one case, an 11 year old boy who was treated with hemodialysis for 2 months prior to receiving a kidney transplant from his father. He cried about being on a restricted diet, but no serious emotional problems were noted. He himself did a good job of managing his fluid restriction.

PREVENTION AND MANAGEMENT OF PSYCHIATRIC COMPLICATIONS

Role of the Nurse Clinician

During the first year of our program, a social worker was a member of the dialysis staff. She evaluated family members as part of the selection process, saw families for follow-up interviews, and assisted with financial problems. During the second year of the program, this work was done by a registered nurse. We found that the dialysis program was complex and often confusing for patients and their families. A renal fellow was their primary physician; however, they were also seen by a bewildering number of attending physicians, fellows, residents, and interns in several specialties. They were given instructions about such items as medication, diet, fluid restriction, and shunt care by physicians, nurses, technicians, and dietitians. They often had complicated financial problems. We decided to create a new position, a nurse clinician who would assist the primary physician in coordinating the patients' medical care, assist the author in the management of certain psychiatric problems, and become the program's specialist in family problems and rehabilitation.

A nurse was selected who had had 10 years of experience in medical nursing and who had an interest in the emotional aspects of medical care. She had had no special training in renal disease or psychiatry. She was given 3 months of training in these specialties by the director of the dialysis program and the author. She learned techniques of interviewing and some techniques of supportive psychotherapy. The nurse clin-

ician makes rounds with the Renal Service and attends the two weekly meetings of the dialysis staff. In addition, she has supervision sessions with the director of the program and the author.

The results of this experiment are encouraging. The nurse clinician has improved coordination of the many details of the patients' care and has improved communication between members of the staff. She interprets physicians' instructions to the patients and their families, and answers some of their questions about medical problems. She coordinates the patients' financial support and vocational rehabilitation.

Family Problems

Hemodialysis is difficult for family members as well as for patients. The repeated stresses, the disappointments, and the uncertainty about the future are shared by spouses.²⁰ Marital relationships are altered, particularly when the dialysand is the husband. His role as the leader and breadwinner of the family is often changed. A decline in sexual functioning is common. He may become dependent on his wife and a spectator in family activities. Shambaugh and Kanter¹⁸ studied the spouses of patients in their program and found feelings of deprivation, hostility, and guilt.

The nurse clinician evaluates important family members as part of the selection process, using a modification of the standard psychiatric evaluation. She assesses their reaction to the patient's illness and the adjustment they are likely to make if the patient is accepted for chronic dialysis. An evaluation is made of the emotional support the patient receives from his family and the help he is likely to receive during periods when his ability to function independently is impaired.

The family members of our patients have not developed severe emotional problems; in almost every case, they have been helpful and supportive to the patients. The importance of support from family members is illustrated by D. F., a 19 year old college student whose family lived in another city. Mr. F. had friends in his dormitory and joined a fraternity; however, these relationships could not substitute for his family. It was impossible for him to prepare meals in his room. He was given permission to use the kitchen in the basement of his dormitory, but the kitchen was a considerable distance from his room. By evening, he was fatigued and the effort of making his own meals was too much for him. Thus he ate at a nearby restaurant and repeatedly went off his diet and fluid restrictions. The problem was aggravated by the conflicts about independence which are a normal part of adolescence. After a severe episode of congestive heart failure, Mr. F. was transferred to a dialysis program near his home so that he could live with his family.

Follow-Up Interviews with Patients and Families

Our patients are seen for monthly follow-up interviews by the nurse clinician to review their adaptation to dialysis. The interviews cover such areas as physical problems, diet and fluid intake, work or school, financial problems, recreational activities, family relationships, and emotional problems. Sometimes patients are interviewed while they are

being dialyzed; at other times, when more privacy is indicated, they are interviewed in an office.

The author and the nurse clinician see patients informally between interviews, and they also see patients for one or a few interviews when problems arise. V. H., a 34 year old housewife, was seen by the author because of tension generated by a conflict between her religion and the need for dialysis. Mrs. H. was receiving religious instruction from the Jehovah's Witnesses. She was attracted by some of their teachings; however, there was an incompatibility between the religion and her treatment. The Jehovah's Witnesses were opposed to the artificial kidney, blood transfusions, and kidney transplantation. They told her that she should let herself die instead of continuing with her treatment. She feared that she would die and would not be able to enter God's Kingdom because she had sinned.

In the interview with the author, Mrs. H. expressed her anger toward the Protestant denomination she had belonged to in the past. Because she was poor, she felt that she could not keep up with the financial obligations that went along with church membership. One of the things she liked about the Jehovah's Witnesses was that they made no financial demands on her. After expressing these feelings, Mrs. H. was able to view her situation more realistically. She wondered who would take care of her seven children if she allowed herself to die, and the author reinforced this concern. He asked Mrs. H. if she felt that God would have given physicians the knowledge and skill to save her life by means of the artificial kidney, if He wanted her to let herself die. Mrs. H. responded by saying that she could go to services held by the Jehovah's Witnesses even though she was not baptized in the Church and did not accept their beliefs about medical care. Her tension was diminished.

More prolonged psychotherapy with the nurse clinician and the author is available when necessary. However, our patients have not required more than a few interviews at times of stress.

Important family members are also seen every few months for follow-up interviews with the nurse clinician. The interviews cover areas similar to those that are covered in follow-up interviews with the patients. The nurse clinician also sees family members informally when they bring patients to the hospital for dialysis. In one case the author saw a patient and her husband together for two joint interviews to discuss marital problems.

Staff Problems

Chronic hemodialysis is not only stressful for patients and their families; it makes unusual demands on staff members as well. Taking care of dialysis patients is a rewarding experience when things go well but a difficult one when things go wrong.⁵ The staff works with a small number of patients and has intensive contact with them over long periods of time. They learn about the patients' lives and get to know their families. They see patients whom they have come to know well and like develop complications and die. The emotional burden is particularly

heavy for the technicians who share the long hours of dialysis with the patients. Emotional upsets in the patients add to the burden.

De-Nour and Czaczkes⁷ noted possessiveness and overprotectiveness toward patients in the technicians in their program. They related these attitudes to underlying hostility on the part of the technicians, and felt that aggression on the part of the treatment team was a major problem. Their experience is consistent with our observations, although staff hostility has not been a problem in our program. Dialysis patients are sometimes unhappy and angry people who vent their frustrations and hostilities on the technicians. While we encourage the technicians to understand the emotional problems of our patients, we also encourage them to accept their own feelings toward the patients, including the angry feelings. We encourage them to express their anger freely in staff meetings.

Our technicians are a skilled and hard-working group. It is hard for them to accept the fact that, despite their best efforts, some patients are too weak to return to work. It is hard for them to accept the fact that they inflict pain on patients despite their efforts to be gentle. For example, they discounted the physical discomfort connected with multiple needle sticks when we began using internal shunts. They talked instead about the patients' anxiety and wondered if tranquilizers were indicated.

We have found it helpful to have a weekly meeting devoted largely to psychosocial problems and rehabilitation. The meeting is attended by nephrologists, the transplant surgeon, the author, nurses, technicians, the dietitian, house staff, and other people who are involved in the care of the dialysis patients. A second weekly meeting focuses on medical problems. This makes it possible for the staff to spend 1 hour a week reviewing the psychosocial and rehabilitation facets of dialysis in depth. The meetings are led by one of the attending nephrologists and the author. Members of the staff are encouraged to bring up problems they have observed in the patients or difficulties they are having in managing patients.

When psychiatric problems are discussed, the rules of the meeting are implicit but definite. The task of the meeting is to improve patient care. The focus is on the patients, and the meeting is not a group psychotherapy session. At times the author can see staff members exhibiting minor emotional problems in their management of patients. These problems are not discussed unless they are interfering with the patients' care in a major way. Sometimes they can be dealt with by translating them into difficulties that the group as a whole is having in dealing with particular patients. In addition to the weekly meeting, a few members of the staff have sought the psychiatrist's help on an individual basis when they are having trouble managing difficult patients.

It is important for the psychiatrist to define his role as a consultant and a participant in the care of the patients rather than as a therapist for the staff. Some people are uncomfortable in the presence of a psychiatrist; they feel that the psychiatrist is "analyzing" them and seeing thoughts and feelings that they wish to keep private. This can be a particular problem in a dialysis program, in which members of the staff

vary considerably in their sophistication about psychiatry, and in which intensive and prolonged contact between staff members and patients evoke strong feelings in the staff.

Short and Wilson²⁰ discussed the strain on physicians of dealing with chronically ill dialysis patients who become "walking textbooks of medicine." They point out the danger of physicians avoiding their own feelings of frustration by denying the magnitude of their patients' medical problems. From the discussion at the weekly meetings, one can see that dialysis has an emotional impact on medical and nursing staff as well as on technicians. Over a period of time, one can see swings of mood in the staff group as a whole. At times denial is prominent, and the staff minimizes the importance of patients' symptoms; at other times, when confronted by several patients who are doing poorly, the mood of the group is one of helplessness and hopelessness. The reality of the situation is somewhere between these two extremes. Our patients are all disabled to some extent, but each of them is able to do something and each of them can get some pleasure out of life. We have found that emphasizing rehabilitation is not only therapeutic for the patients; it also improves the morale of the staff.

The adaptation of the patients in our program has in general been good. We sometimes wonder how patients can accept the extraordinary stresses of the dialysis regimen and problems in multiple organ systems without decompensating emotionally; yet, we have had few serious psychiatric complications.

Two factors have helped to reduce the number and severity of psychiatric problems in our program. The first is an attitude of hopefulness on the part of the staff. Staff members have developed the attitude that they can do something to help each of our patients, no matter how serious the problems are. Goals are individualized for each patient and are flexible. The medical status of dialysis patients changes frequently, and our goals change accordingly. In some cases the goals are ambitious, and realistically so. We can return some of our patients to a relatively normal life. They are able to work and go on vacations. In other cases, patients can achieve only a limited degree of rehabilitation, but they can still get pleasure from relationships within their family and visiting with friends. In a few cases, we can offer little more than some degree of comfort and the security that comes from knowing that, no matter what happens, they will be cared for.

N. R., a 34 year old insurance auditor, developed a subphrenic abscess following nephrectomy. Despite antibiotics and several attempts to treat the abscess surgically, the wound continued to drain for many months. Mr. R. had to come to the hospital daily to have his dressing changed, and a transplant was out of the question. He was too weak to work. He had been an amateur painter, but hypertensive retinopathy had produced a partial blindness which interfered with this hobby. To make matters worse, his marriage was a very bad one. His wife ignored him, and he had to cook for himself. Mr. R. had six brothers and sisters, but they lived in a distant state. Despite the apparent hopelessness of his case, the staff did not withdraw from Mr. R. The dialysis unit became

a home to him, and the nurses and technicians became the warm and interested family he did not have outside the hospital.

The second factor is the accepting attitude of the staff toward emotional problems that do arise. Our staff has a rather high tolerance for patients expressing themselves about their unhappiness. This is particularly important with respect to angry feelings directed at the dialysis program or the staff. R. J. was a 57 year old engineer who was transferred to our program because he was dissatisfied with hemodialysis at another hospital. He was a vice-president of a corporation and had been successful and productive in his work. This hard-driving and compulsive man was an extremely difficult management problem. He insisted on maintaining his position of importance and demanded personal attention from the director of the program. He berated the technicians mercilessly, swearing at them and calling them "incompetent" and "stupid." At times he became paranoid, and he threatened to sue a surgical resident for "giving him a wound infection" at a shunt site. He was not well enough to return to the demanding work he had done, but he could not accept this. Instead he blamed the dialysis program for not keeping his hematocrit high enough, and for keeping his blood volume too low.

During the first 6 months that this patient was in our program, the technicians required much support from the director of the program and the author. The staff was encouraged to express their justifiable anger toward this patient in staff meetings. The patient was encouraged to direct his complaints to the physicians rather than to the technicians. The physicians were in a better position to answer his questions; and since they did not have to spend as much time with him as did the technicians, it was easier for them to accept his anger. It took about 1 year for this patient to adapt successfully to our program. In time he came to accept the fact that, despite multiple transfusions, his hematocrit remained low. He accepted the fact that we were giving him the best care we could and that his rehabilitation was limited not by our incompetence but by his disease.

The attitude of the technicians was an important factor in his successful adaptation. They came to realize that Mr. J's. attacks on their competence reflected his own feelings of incompetence and uselessness. They came to understand that he blamed his failure to return to work on poor medical management because he could not accept the fact that he was too sick to be an effective executive. They also recognized that it was not their responsibility to make this patient healthy and happy. Rather it was their responsibility to give him a technically good dialysis. They became less involved in trying to please him, for it was clear that, for a period of time, this patient would not be satisfied no matter what they did. While Mr. J. remained a difficult and sometimes unpleasant patient, his attacks on the program and the technicians diminished greatly in frequency and intensity.

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Renal Transplantation

Certain Immunological Considerations

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Immunologic aspects of renal transplantation are considerably more complex and restricting than are the actual technicalities of the procedure. While clinical renal transplantation has certain frustrating limitations, such as the lack of ready availability of donors and the necessity for a large, complex, and expensive system of dialysis in order to support patients in need of kidney transplantation, the necessary equipment and skills are now readily available, and problems presently center in the provision of an immunologically acceptable donor-host relationship. The nature of transplantation antigens of man and the immunogenetics of that system, and the most effective means of manipulation of the immune response to those antigens are central issues awaiting solution.

Despite these problems and limitations, wide experience has been gained in renal transplantation. At the present time, the overall long-term success of this procedure is well above 50 per cent, and approaches 90 per cent when carefully chosen siblings volunteer as kidney donors.³⁶

This presentation will deal with practical aspects of the transplantation antigen system in man, the immunosuppression of rejection, and clinical problems associated with rejection and immunosuppression.

TRANSPLANTATION ANTIGENS

Human transplantation antigens are located on all cell walls except those of the erythrocyte.⁸ A number of investigators have recently reported the results of their studies following solubilization of the antigenic

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material on cell surfaces, and, while many differences in methods, results, and interpretations of the data exist, there is general agreement that the materials obtained are proteins in association with carbohydrates or lipids.^{10, 21, 24}

These chemical materials, seemingly unique to each individual, reflect the genetic diversity which exists in the human population. In a recent review of the literature, Russell and Winn have pointed out that "the enormous potential for variation in amino acid sequence could readily account for the extensive chemical and thus antigenic polymorphism that exists within each species."³⁵ These authors have also pointed out that if antigenic specificity and polymorphism were to be related to the carbohydrate moieties of the antigens instead of to the proteins, it would be difficult to assume the presence of enough enzymes, each acting upon a different substrate, to produce such a large diversity of carbohydrate specificities. Kahan has suggested that transplantation antigens represent direct polypeptide transcriptions of the histocompatibility loci. Solubilization, isolation, and characterization of the HL-A antigens is an important achievement, since it may be possible to induce specific tolerance with the use of these agents.

Immune reactions related to transplantation antigens take place on cell surfaces, since these antigens are located almost entirely on outer cell membranes. Subcellular fractions seem to be only minor contributors to transplantation antigen localization.³¹ Quantitative differences of antigen distribution in various tissues have been reported, with spleen and other lymphoid tissue having the greatest concentration, parenchymal organs somewhat less, and central nervous system and muscle tissue the least.² Antigens are also detectable in tissue culture cell lines.¹¹

The major transplantation antigens of man, analogous to the H-2 antigens of mice, are controlled by one complex locus, the HL-A locus.⁷ Determinations of HL-A antigens form the basis of tissue typing in man, and while it is recognized that non-HL-A antigens participate to some extent in transplantation rejection reactions, the actual importance of the additional antigens is not known and these are generally regarded as "weak."¹⁶

PATHOPHYSIOLOGY OF THE REJECTION REACTION

Both cellular and humoral antibody responses are important in the rejection of kidney transplants in man. In the absence of previous exposure to the antigens of the transplanted kidney (presensitization), the rejection reaction appears to be due largely to the activity of sensitized small lymphocytes which have been derived from the recipient's population of thymus-dependent lymphocytes.^{5, 14} Transplantation antigen material may be released into the renal venous blood to reach these cells in the circulation or lymph nodes,²⁹ or cells from the bloodstream will infiltrate the parenchyma of the kidney and become sensitized to foreign antigen present on endothelial and renal cell surfaces.³⁸ Upon sensitization, these cells become transformed into blast cells which divide and

then appear to exert a direct destructive effect upon the kidney *in situ*.⁴³ Infiltration and multiplication of mononuclear cells within the transplant begins almost immediately and, if unchecked by immunosuppression, will cause necrosis (rejection) of the kidney as early as 10 days following transplantation.

Even when donor and recipient are distinctly incompatible for the HL-A antigens, it is frequently possible to suppress the rejection reaction with appropriate drugs. In those individuals in whom acute rejection episodes have been reversed, biopsies taken of the kidneys months or years after transplantation have frequently revealed vascular changes of an obliterative nature.³² These vascular changes are associated with the deposition of immunoglobulins and complement within the vessel walls, with subsequent intimal proliferation and disruption and reduplication of elastica.²⁰ In a series of patients reported by Jeannet, all recipients with vascular lesions in postoperative biopsy specimens had developed humoral antibody detected by mixed agglutination, leukocytotoxicity, or leukoagglutination techniques.¹⁷ Vascular lesions are typical of "chronic rejection" and thus appear to represent donor-recipient histoincompatibility, which is manifested by the production of serum antibody despite successful suppression of the acute cellular type of rejection reaction.

These findings of vascular lesions in chronic rejection led Kincaid-Smith to recommend the use of anticoagulants and dipyridamole in order to prevent the progressive narrowing and thrombosis of vessels which occurs in response to the irritating effects of antibody and complement deposition. She has demonstrated a striking reduction and modification of vascular lesions with the use of these drugs.²²

Of more immediate importance, however, is the development of humoral antibody towards transplantation antigens before transplantation is undertaken (presensitization). This circumstance is seen most commonly in patients who have received multiple whole blood transfusions, but may also occur in patients who have rejected a transplant or in multiparous women who have become immunized against paternal antigens of the fetus. In a recent study in our laboratory of 100 patients on chronic dialysis, it was found that 80 per cent of those who had received whole blood transfusions had developed antibody towards transplantation antigens, as detected by lymphocytotoxicity tests against unrelated individuals.⁶ If, in fact, the recipient has been presensitized toward and has developed antibodies against transplantation antigens which are shared by the kidney donor, a hyperacute rejection reaction will take place, with immediate thrombosis and loss of viability of the organ.⁴⁴ This type of rejection reaction, a "white-graft" reaction, occurs when the humoral antibody reacts with antigens on vascular endothelium and, with the participation of complement, causes thrombosis.

This immediate sort of rejection reaction can be avoided by preoperative crossmatching, testing the recipient's serum against the donor's white blood cells. A positive reaction, even in the presence of reports of excellent compatibility on the basis of serologic tests, certainly contraindicates performance of the transplant. A negative crossmatch

test in a recipient who is known to be presensitized toward a certain percentage of the population does not necessarily indicate that the recipient is not sensitized toward that particular donor, since the antibody toward those particular antigens may have decreased in titer at that moment and be undetectable by the standard method of performance of crossmatch, that of a lymphocytotoxicity test.

We have often found in retrospective studies that a recipient might have positive reactions to the cells of a donor at one time and have completely negative reactions toward the cells of the same donor when tested several months later. This is a misleading negative test, however, since the recipient is obviously sensitized toward that donor's transplantation antigens, and an anamnestic response with a rapid rejection reaction occurring within the first week following transplantation is to be expected. This "second set" reaction would be difficult if not impossible to control with ordinary immunosuppressive measures. Perhaps with more sensitive methods, such as mixed agglutination, a low-titered antibody could be detected.²⁶

It seems most important to avoid sensitization of potential recipients with whole blood transfusions. In a group of 20 dialysis patients who have received only leukocyte-poor blood, prepared by removal of the buffy coat with saline washes, we were unable to detect lymphocytotoxic antibodies.⁶ Of course, the number of transfusions given all patients awaiting transplantation should be reduced to a bare minimum.

HISTOCOMPATIBILITY TESTING AND DONOR SELECTION

Since peripheral blood lymphocytes provide a convenient and representative sample of the HL-A antigens of each individual, most methods of histocompatibility testing rely on serologic typing of lymphocytes or in vitro reactions of lymphocytes in culture with subsequent pairing of donor and recipient on the basis of similarity of their reactions. When reliance is placed upon these methods in choosing a donor from within the recipient's family, good results can be predicted, and it is quite generally accepted that tissue typing is of paramount importance in choosing the best related donor.¹⁸

Many technical problems exist in the typing of cadaver donors, and since the HL-A antigen system is very polymorphic, the data is not nearly as clear in supporting the contention that histocompatibility testing is a valuable adjunct to pairing of unrelated donor and recipient. However, in studies in which this has been possible and in which the technical problems have been largely resolved, preliminary reports show significantly improved results when donor and recipient, even though unrelated, are matched for HL-A antigens according to the histocompatibility testing techniques which are commonly used.^{4, 40}

In a family, the selection of a donor may be considerably simplified by analysis of the segregation of HL-A antigens within the members of the recipient's family.⁴⁶ Despite the complexity of the HL-A locus, and the many alternative alleles which exist, the HL-A locus behaves as a

single chromosomal region (allele) transmitted as a unit from parents to offspring (Fig. 1). The distribution of maternal and paternal alleles to the siblings can often be determined, and it will be found that one fourth of the siblings have received the same maternal and paternal chromosomes and will be identical for HL-A loci. Another 50 per cent of siblings will share one but not the second parental chromosome (as is the case with either parent, and child). Antigens produced by the non-shared chromosome will then represent the degree of mismatch. In the remaining one fourth of siblings, both HL-A complexes will be different and these siblings will be no better "match" for one another than would any two individuals in the random population. Assuming ABO compatibility, siblings who are HL-A identical to the recipient are ideal donors, since no major transplantation antigens are introduced. Any disparity between these siblings is due to non-HL-A ("minor") antigens.

When donor and recipient are HL-A identical siblings, rejection crises have not been observed and excellent long-term function is the rule. It is not possible to withdraw immunosuppression from these patients as a routine, since, if this is done, subsequent biopsies show infiltration with mononuclear cells, typical of a mild acute rejection reaction.³⁷ Renal function is seldom altered and may remain entirely normal for many months despite this infiltrate, and detection of the mild rejection episode will be dependent upon biopsy alone. Non-HL-A antigens are responsible for these mild rejection reactions.

Renal function has been studied in a series of related-donor transplants in which the donor shared with the recipient one or both parental HL-A loci, and the donor's non-shared chromosome did not appear to produce HL-A antigens absent in the recipient. In these patients, renal function as measured at 6 month intervals was consistently in the upper tenth percentile as reported by the Human Kidney Transplant Registry.¹⁹ Biopsy specimens, as well, have been normal in these patients. Donor selection of this sort, using the technique of genotypic analysis of the family, becomes a most useful method.

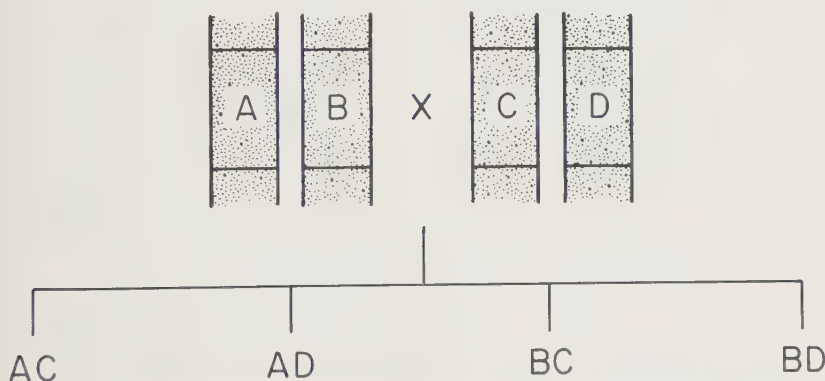


Figure 1. Distribution of maternal and paternal HL-A complexes among offspring. There is a 25 per cent chance that two siblings will have identical HL-A complexes, a 50 per cent chance that the siblings will share one HL-A complex, and a 25 per cent chance that the HL-A complexes of the two siblings will be entirely different.

If donor and recipient are unrelated, or if family analysis is not possible, reliance must then be placed on matching of the donor and recipient through comparisons of reactions in serologic tests. Antisera, obtained from multiparous women or following purposeful immunization of volunteers with leukocyte injections, are used to identify the HL-A antigens. The method most commonly employed is a cytotoxic test using peripheral blood lymphocytes. Several modifications of this test have been described,^{1, 27} but all rely upon preparation of a pure suspension of lymphocytes which are then exposed to the test panel of antisera in the presence of complement. Lysis of cells by a particular antiserum, as measured by uptake of a vital dye or release of a radioactive tag, is a positive reaction.

The HL-A locus is complex, composed of at least two "sub-loci," and a number of alternative alleles exist⁹ for each of the two subgroups in the HL-A locus (polymorphism) (Fig. 2). Owing to this polymorphism, it is unlikely that two individuals in the random population will share identical sets of HL-A antigens. It is also unlikely that any antibody produced by multiple transfusion from random donors or even by multiple pregnancies will be directed against only one of the HL-A antigens (monospecific); in fact, most typing sera produced by any means will react with more than one antigen and are therefore polyspecific. The lack of monospecific typing sera has been a major limiting factor in definition of the HL-A antigens. Cross reactions are common between

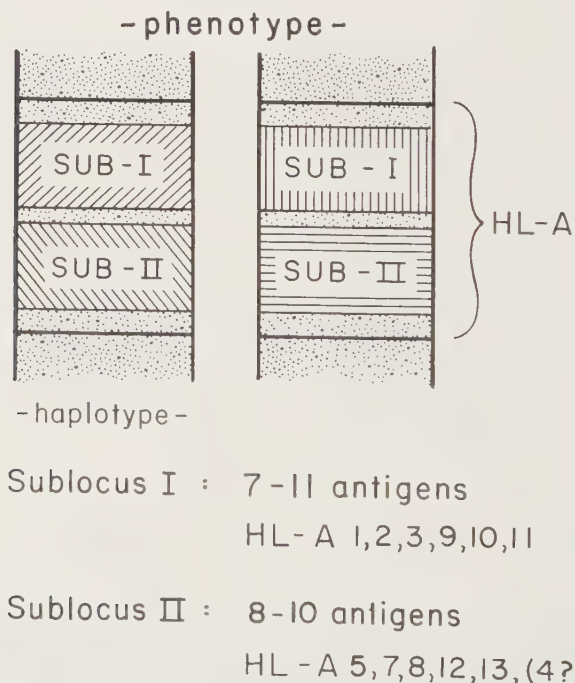


Figure 2. The HL-A locus in man.

several of the antigens, and the precise significance of the antigenic groups is not clear.³

The genetic determinant of the antigens, the HL-A locus, is considered to be composed of two subloci, each of which has a segregant series of alternative alleles. HL-A antigens 1, 2, 3, 9, 10, and 11 are associated with the first sublocus ("LA" segregant series). An individual will have any two of the antigens of this first series, or he might be homozygous, in which case only one antigen will be detected. Several additional alleles are also thought to be present in this series but these have not yet been defined. The second sublocus (the "4" or "7" segregant series) is associated with HL-A antigens 5, 7, 8, 12, 13, and a number of additional as yet unclassified specificities. An individual may similarly have only two antigens from this second series, or a total of four HL-A antigens as a maximum. Certain of these antigens seem to be frequently associated with one another, particularly HL-A antigens 1 and 8, and 3 and 7.³⁴ The HL-A antigens produced by one HL-A locus are termed a haplotype; the sum of an individual's two haplotypes is his phenotype.

Since the number of possible combinations is so great, phenotypic identity among unrelated individuals is rare. It is for this reason that large scale cooperative programs have been developed so that a large pool of recipients is available to choose from in order to find the individual recipient(s) most closely matched to each available cadaver donor. Because suitable cadaver donors are infrequent and the number of potential recipients constantly exceeds the supply of organs for transplantation, such a recipient pool will make most efficient use of the cadaver organs and provide the greatest chance for a successful transplantation procedure on the basis of donor-recipient compatibility. Although the number of transplantation procedures which have been done with a cooperative system of this type is small, the results have been reported to be considerably improved over random cadaver transplantation.⁴²

The success of such a program is totally dependent upon the size of the recipient pool, and when short-term organ preservation becomes practical, a nationwide recipient pool is a distinct possibility. Refinements in typing of the potential cadaver donor are also needed in order to make this donor-recipient pairing a reliable test.

As currently practiced in our laboratory, a pool of 170 potential recipients in the Chicago area is first examined for ABO compatibility with the donor. Recipients are then selected who are compatible with the donor for all of the known HL-A antigens. A final recipient selection is made by comparing all serological reactions between donor and recipient, one by one, and computing a coefficient of correlation (r) which then ranks recipients as to their similarity to the donor. Coefficients of correlation greater than 0.5 are highly desirable.

An occasional donor will be found who has a major antigen mismatch with all available recipients. It would therefore be desirable to ascertain the strengths of individual antigens, since incompatibilities for certain of the antigens might be overcome by appropriate immunosuppression with an acceptable clinical result. The criteria of donor

and recipient compatibility for HL-A antigens could then be relaxed. In this event, the chances of matching unrelated donors and recipients would be greatly increased, and maximal use of the donor organs would become a more likely possibility. Information of antigen "strengths" will be obtained through observations of the clinical courses of transplants done across such incompatibilities, particularly when these are done in families where it is known that one chromosome is shared between donor and recipient and antigenic incompatibility for a single antigen only is more likely. However, as pointed out in a recent review of this subject by Hildemann,¹⁶ presensitization of the recipient to even a weak histocompatibility antigen will seriously shorten allograft survival. Blood transfusions or other means of immunization would therefore make even the weakest of HL-A antigens become strong in the context of adversely affecting graft survival. Once again, the avoidance of presensitization becomes obvious.

IMMUNOSUPPRESSION

Since ordinary rejection reactions result from activity of small lymphocytes, attenuation of rejection has been attempted through depletion of the recipient's lymphocyte population or through chemical suppression of synthetic processes and cell multiplication. Chronic thoracic duct fistula,¹² sublethal total body irradiation,¹⁵ and extracorporeal irradiation of the blood⁴⁵ are effective adjuncts in immunosuppression. Corticosteroids are similarly effective in reducing the population of lymphocytes. Antilymphocyte serum, an antiserum prepared in a species foreign to human lymphoid cells, may also exert its immunosuppressive effect through removal or inactivation of lymphocytes in the circulating blood.²³ The immunosuppressive effects of antilymphocyte serum have been striking in the laboratory, but clinical information obtained from well-controlled studies in man has not yet become available.

Metabolic inhibitors, particularly azathioprine, a derivative of 6-mercaptopurine, remain the basis of immunosuppression, and are commonly used alone or with prednisone and other drugs such as the actinomycins. By careful adjustment of azathioprine dosage in order to avoid leukopenia, many complications related to infection can be avoided, so that most patients on routine immunosuppression do not need to be isolated. Chronic administration of immunosuppressive drugs to the recipient before transplantation has no advantage and is unnecessarily hazardous.

When transplantation is an elective procedure, azathioprine and prednisone are begun on the day prior to operation, in doses of 5 mg. per kg. These drugs are continued postoperatively, azathioprine in doses of 1 to 3 mg. per kg. per day, and prednisone doses being adjusted downward as tolerated.

Since many patients require large doses of prednisone on a daily basis for long periods of time, some of the most serious complications of transplantation have occurred as a result of the side-effects of chronic

prednisone therapy. Administration of prednisone on alternate days has significantly reduced troublesome side-effects and has proven to be as effective in control of certain disease processes as daily therapy.²⁵ Reed et al.³³ have reported a successful alternate day regimen after renal transplantation, and we now use this regimen routinely in all patients requiring more than 10 mg. of prednisone per day as maintenance therapy.

Both of these methods of immunosuppression, that is, the anti-metabolites and reduction of the small lymphocyte population, are non-specific. A more specific mechanism of immunosuppression, such as immunological enhancement or the induction of specific tolerance, is highly desirable. Evidence exists that in other species, enhancement of an organ graft does occur (protection of the graft by specific antibody).¹³ The animal retains its general capacity to respond to those specific transplantation antigens and can respond normally to all other antigenic stimuli as well. Evidence also exists that specific immunological tolerance to transplantation antigens can be induced in the adult animal²⁸ (specific nonresponsiveness to a single antigen), and the induced lack of responsiveness of certain kidney transplant recipients towards their donors' cells suggests that it may also be possible to induce tolerance in man. Soluble transplantation antigens may have their greatest importance in this particular area.

Other experiments dealing with antibody suppression by the use of antibody and antigen may also prove promising in clinical transplantation.³⁹

CLINICAL PROBLEMS

When the successes and failures following renal transplantation are summarized, it becomes quite clear that patients receiving kidneys from related donors have done much better in all respects than have patients receiving kidneys from cadaver donors. Reasons for these differences are many, and include the inevitable occasional occurrence of irreversible acute tubular necrosis in cadaver transplants. It is clear, however, that the most important factor in successful transplantation is the genetic similarity between the donor and recipient. The complexities of the HL-A antigen system and the uncertainties present in typing precisely for all antigenic specificities have made it difficult to pair unrelated donors and recipients with the same degree of accuracy as can be done by genotyping a family.

The incompatibilities, detected or not, between donor and recipient are responsible for the rejection reactions which occur, and rejection, in turn, seems to be the basis for the large majority of complications which occur following transplantation. Ureteral leaks or stenosis, narrowing of the arterial anastomosis, hypertension, proteinuria, and pyelonephritis are usually the result of a rejection reaction. Infectious complications, one of the more common problems following transplantation, are related to immunosuppressive drug regimens and are most

troublesome when rejection reactions make it necessary to immunosuppress the recipient heavily.

While renal transplantation has been relatively successful in many children, the immunosuppressive drug regimen necessary to inhibit rejection has seriously limited growth and development. The actual achievement of well-being for children is not as good as one would desire.¹¹

Donor and recipient pairing for the nearly complete compatibility that seems to be necessary for superior function and restoration of optimal health is presently difficult to achieve. Therefore, other means of specific immunosuppression, such as the induction of tolerance or enhancement, would be the next logical step. Heavier immunosuppression of a nonspecific nature is undesirable from many points of view and may become particularly dangerous if it is true that profound immunosuppression renders the individual more susceptible to the development of neoplastic disease.³⁰

SUMMARY

Donor-recipient pairing on the basis of histocompatibility testing seems to be critical in assuring a successful renal transplant. Within families, genotyping and selection of HL-A identical sibling donors is the ideal situation. When donors and recipients are unrelated, the problem of "matching" on the basis of histocompatibility testing is more difficult, and a large pool of recipients should be available so that a recipient who is most compatible with the unrelated donor may be chosen.

Immunosuppression of a nonspecific nature is accomplished with a combination of antimetabolites and measures to decrease the lymphocyte population. Further attempts to induce enhancement and tolerance, so that immunosuppression will be specific, are in order.

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Human Renal Transplantation

Progress in Organ Preservation In Vitro

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Advances in organ grafting have been extraordinary over the past decade. Allograft rejection mechanisms, methods for modifying the reaction of the recipient organism, and the identification and genetic control of histocompatibility antigens are considerably better understood. Despite these developments, however, broader application of this proven therapeutic modality is restricted. Paramount among the factors restricting more wide-scale kidney transplantation are the limited number of suitable donor organs available, and their rapid deterioration after excision.

The introduction of a simple effective method of preserving cadaver kidneys in vitro would probably double the number of human renal transplants that could be carried out, if such a method were uniformly understood, accepted, and applied by transplant centers throughout the world. Successful organ preservation, by increasing the number of potential cadaver kidneys, decreasing the need to use living donors, and providing sufficient time intervals for air transportation of transplantable kidneys when necessary, would overcome a major barrier now confronting us.

METHODS OF IN VITRO ORGAN PRESERVATION

Several different methods have been described for the preservation of whole organs in vitro. The simplest means of categorizing these methods is to classify them according to their physiologic effect. Generally, the approach to preservation of a whole organ is by (1) implementing measures to decrease metabolic activity of individual cells of that organ, or (2) supplying vital substances to the "deprived" organ by perfusion.

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PRESERVATION BY DECREASING METABOLISM

Resistance of an organ to injurious ischemia consequent to interruption of vital needs may be increased by four basic methods as follows: (1) hypothermia, (2) hyperbaria, (3) freezing, and (4) pharmacologic agents.

Hypothermia

Hypothermia is common to most methods of organ storage, since it is simple and effectively lowers metabolic activity, thereby decreasing the nutritional and respiratory needs of the organ. Hypothermic renal storage, originally shown to protect anoxic kidneys by Bogardus and Schlosser,² is an attractive storage modality to employ because of its simplicity of induction. Since then, reports in the literature describing hypothermic organ protection have been numerous, with marked variations in attitude regarding what temperature is best, what the composition of the perfusate should be, how long hypothermia can afford protection, and the most effective method of inducing hypothermia. Schloerb et al.²³ reported short-term kidney preservation by simple immersion in cold media. These investigators demonstrated the benefit of hypothermia with 8 hour storage in situ, and carried out immediate contralateral nephrectomy.

The depression in metabolism is exponentially related to temperature reduction, with oxygen consumption being reduced to 16 per cent of normal at 20° C., and to about 5 per cent of normal at 10° C.¹¹ Obviously, then, a substantial protective effect can be achieved even by modest hypothermia; however, longer successful preservation, utilizing hypothermia alone, occurs when lower temperatures (in the area of 2° to 4° C.), are used. Still, caution must be exercised to avoid temperatures below 0° C. because of ice crystal formation in the renal parenchyma.

Some investigators feel that hypothermic storage is effective for periods up to 24 hours, depending on the organ and the animal species; but for the most part 12 hours is the outside limit that a whole organ can be maintained in vitro by cooling alone, according to most authorities.

Rapid cooling of an excised kidney is most important to minimize ischemic damage and probably is best induced by perfusion or core cooling. Pegg extended canine kidney storage from 17 hours (surface cooling) to 24 hours (perfusion cooling), demonstrating the advantage of the latter by shortening the warm ischemic interval.²²

There is still no agreement about which solution is most satisfactory for perfusion of a kidney. Evidence would suggest, however, that a perfusate of isotonic or slightly hypertonic composition combined with a colloidal substance, an anticoagulant, and a vasodilator is best (Table 1). In our laboratory, we have used a balanced salt solution with low molecular weight (40,000) dextran, procaine, and heparin with gratifying results.¹⁶

Initial flushing of an excised kidney designed for transplantation is important. Perfusion removes red blood cells and other debris which otherwise would cause capillary sludging and also break down with the

Table 1. *Requirements of a Perfusate During Hypothermic Storage*

Isotonic or slightly hypertonic composition
A colloidal substance
An anticoagulant
Vasodilator
Buffer
Antibiotic

elaboration toxic metabolites. The addition of an antispasmodic such as procaine to the perfusate is important, in that it probably improves micro-circulatory flow during the early stages of cooling, even though the vasodilators have variable effects below 20° C. and below pressures of 90 mm. Hg. Heparin is the most effective anticoagulant and is primarily important immediately after devascularization to prevent coagulation and plugging of small vessels.

Although hypothermia alone will never be a solution for long-term organ banking, it has proved to be very useful for short-term storage and as an adjunct to other methods.

Hyperbaric Oxygen

Manax and Lillehei¹⁹ first reported the use of hyperbaric oxygen in combination with hypothermia for the preservation of kidneys. By this technique, canine kidneys were successfully preserved in vitro for 24 hours and when reimplanted, such kidneys could sustain life and health of recipient animals after delayed contralateral nephrectomy. Lempert¹⁰ reported that dogs could survive after reimplantation of kidneys preserved for 24 hours under hypothermia and hyperbaric oxygen, even in the face of immediate contralateral nephrectomy. Experiments designed to delineate the role of hyperbaric oxygen in organ storage have employed inert gases under increased atmospheric pressures plus hypothermia.

Studies comparing the effects of hyperbaric oxygen, hyperbaric helium, and hyperbaric nitrogen indicate that the increased gaseous pressure in itself is an important factor contributing to success of this method.¹⁵ It is interesting to note that hyperbaria alone, without adjunctive hypothermia, is of no benefit whatsoever.

The precise mechanism of action of hyperbaria in combination with hypothermia is not understood. The most likely explanation is that hyperbaric oxygen is toxic at the pressure used, and that this toxicity is partially responsible for inhibiting metabolism governed by enzymes containing sulfhydryl groups. Another possibility is that cell swelling, the final common pathway in tissues deprived of oxygen, may be delayed or minimized in a high pressure environment.⁵

Freezing

The logical extension of hypothermia for organ preservation is freezing. However, total freezing is uniformly lethal to adult cells in the mammal, with the exception of the erythrocyte. There are a few chemical

agents, most notably glycerol and dimethylsulfoxide (DMSO) which, by virtue of colligative or water-binding properties, confer protection against freezing injury. These cryoprotectants have permitted successful freezing of sperm, skin, red blood cells, and fetal kidney cell suspensions.¹⁹ Although such tissues may be successfully frozen with the addition of cryophylactants, various problems in freeze-thaw procedures thus far have precluded successful freezing of a whole mammalian organ.

Pharmacologic Agents

Table 2 categorizes the various pharmacologic agents that are used in organ preservation. The cryoprotectants, glycerol and DMSO, are described above. Vasodilators are of especial benefit during continuous perfusion procedures when vasoactive substances may accumulate. Probably the most common vasodilator used clinically is procaine; however, other agents such as antiepinephrine substances, serotonin antagonists, and antihistamines fall into this category. Diuretics seem to be of some benefit. Their probable value is to "prime" solutions prior to renal storage, inducing diuresis, which presumably maintains intratubular volume and pressure, thereby counteracting edema. They may also serve to dilute toxic products and precipitates which would obstruct subsequent tubular flow.

A variety of metabolic inhibitors have been used with varying degrees of success, most commonly, magnesium sulfate, antithyroid preparations, sodium fluoride, and organic mercurials. Perhaps the most popular of the pharmacologic agents used in organ storage are membrane stabilizing agents, especially chlorpromazine.⁶ Corticosteroids and

Table 2. *Pharmacologic Agents for Whole Organ Preservation*

Inhibition of metabolism
Magnesium sulfate
Chlorpromazine
Sodium fluoride
Thiouracil
Membrane stabilizers
Chlorpromazine
Corticosteroids
Chloroquine
Cryophylactic agents
Glycerol
DMSO
PVP
Vasodilators
Procaine
Phenoxybenzamine (Dibenzylamine)
Diuretics
Anticoagulants

chloroquine also fall into this category. These agents have been used in an effort to delay or reduce the untoward effect of anoxia on cell membranes, which may be two-fold: cell swelling because of plasma membranes leaky to sodium ion, and disruption of lysosomes with release of acid hydrolases. Membrane stabilizing drugs diminish both of these damaging effects.²⁸

None of the drugs in these categories is dramatically effective in itself, but they are all beneficial when used as adjuncts to enhance the quality of storage.

METHODS OF INCREASING VITAL SUPPLY TO TISSUES

All storage systems attempting to supply vital ingredients to organs employ some form of continuous organ perfusion. The methods of perfusing whole organs may be classified as follows: (1) biologic perfusion; (2) pump-oxygenator systems—whole blood, hemodilution, acellular solutions; (3) extracorporeal perfusion and total cardiopulmonary bypass.

Biologic Perfusion

Cross-circulation, accomplished by temporary connection of the vasculature of an organ to the circulatory system of another animal, is one method of keeping an organ viable. Although this method offers no hope of long-term preservation, it has been applied both experimentally and clinically.

Total body perfusion and oxygenation by means of cross-circulation from a healthy donor is one method of completely isolating the heart of a diseased recipient, and this method has been used clinically.¹² The distinct advantage of this system over mechanical oxygenation is that it provides the recipient with other normally functioning donor organs during cross-circulation.

Pump-Oxygenator Systems

Any pump that can move fluid in one direction can serve as a substitute pump for blood. The best way to apply this principle to the human circulatory system is to imitate nature; therefore, the pump must produce a pulse wave. Thus, by using a suitable pump oxygenator and perfusing solution, we may perfuse isolated organs, study their behavior *in vitro*, and evaluate viability and function of the perfused organs after replantation. A system designed to perfuse isolated organs must have a workable pump, a manometer to record pressure, an organ chamber, an oxygen source, a reservoir and oxygenator, and, finally, a filter. The most critical factors to be considered here are the perfusing pressure, temperature, and composition of the perfusing solution. Individual perfusing agents are considered below.

WHOLE BLOOD. Loebell¹³ was the first to perfuse an isolated kidney preparation using defibrinated blood. Subsequently, numerous investigators perfused canine kidneys with whole blood (Bidder; Bainbridge

and Evans; Starling and Verney; Winton), but at best, only very limited success was obtained.²⁶

Most investigators now agree that isolated kidneys perfused with blood are rapidly damaged since perfusing blood buffers poorly, readily hemolyzes, and produces hemoglobin casts and bloody urine upon revascularization. Long¹⁴ described the occurrence of erythrocyte aggregation in organs undergoing prolonged extracorporeal perfusion, the subsequent formation of small blood vessel thrombi, vascular obstruction, and, finally, decreased blood flow to that particular organ.

DILUTED BLOOD (HEMODILUTION). Telander²⁷ has reported that fresh heparinized blood diluted with a balanced salt solution is also damaging and cannot maintain renal function during prolonged isolated perfusions. Such kidneys show marked parenchymal changes with tubular edema and disintegration. Humphries, however, has perfused kidneys for 48 hours *in vitro* using diluted autologous blood, followed by autotransplantation.⁸ Four of seven dogs receiving such kidneys survived and remain healthy even after contralateral nephrectomy.

ACELLULAR PERFUSATES. Certain common problems attend isolated perfusion of organs: arterial spasm; inadequate flow rates; inadequate perfusion pressures; cellular swelling within the organ and osmotic derangement resulting in abnormal electrolyte shifts; and decreased capillary blood flow and increased vascular resistance. All of these cause tissue hypoxia.

At hypothermic temperatures, hemoglobin is unnecessary to meet oxygen requirements and, indeed, may be detrimental. With increased solubility of oxygen attending low temperatures, plus reduced metabolic activity, tissue oxygenation is adequately accomplished with reasonable flows and pressures with hemoglobin-free perfusates. Survival of kidneys after perfusion with diluted plasma to normalize viscosity has been reported for up to 3 days.⁹ Particle obstruction still occurs, however, and is the factor causing eventual failure with plasma perfusates, since albumin-saline or dextran-saline solutions will flow for 1 week or longer. Proteins and lipoproteins are denatured by air-fluid interphases which will cause particle obstruction. Still, lipoproteins become unstable with changes in temperature, and fats start solidification at 15° C. These observations probably explain the inability to achieve greater than 72 hour survivals with diluted plasma.

Belzer may have solved this problem by cryoprecipitation and millipore filtration of plasma which remove most of the unstable lipoproteins and eliminate intravascular lipid deposits so strikingly evident after perfusion with untreated plasma. This technique to date has provided the best reported results with canine kidney storage, allowing immediate contralateral nephrectomy after 72 hour *in vitro* perfusions.¹

Intracellular edema results from both hypothermia and anoxia. Hypoxia causes edema by interference with cellular respiration and physiologic electrolyte gradients across the cell membrane. The precise mechanism by which hypothermia causes cellular swelling is not known. Still, hypothermia remains the most important factor in organ preservation.

Since low molecular weight (40,000) dextran (LMD-40) protects against injurious cell hypoxia, such as in shock, its reported value in organ preservation may be a consequence of maintaining capillary circulation.⁷ Certainly, the beneficial colloidal osmotic effect of LMD-40 attests to this fact. Perhaps this agent is of value because it interrupts the sequential chain of events occurring from the onset of anoxia (or hypoxia) to an organ until anaerobic metabolism is realized.

Extracorporeal Perfusion and Cardiopulmonary Bypass

Complete heart-lung bypass with extracorporeal perfusion cooling provides both hemodynamic and metabolic support for visceral donor organs. There are several reports of donor kidneys obtained from patients dying during open intracardiac surgical procedures having been allo-transplanted successfully into recipients, with immediate renal function.

Marchioro²⁰ described a technique of extracorporeal cadaver perfusion using a disposable bubble oxygenator, a single DeBakey pump, and a heat exchanger. By such a method, he obtained functional renal allografts up to 14 hours postmortem. Moreover, a major advantage of total body perfusion and cardiopulmonary bypass is the provision of multiple organs for clinical allografting from a single cadaver.

In conclusion, although considerable progress has been made in recent years in organ preservation (even with recent reports of 5 day preservation by extracorporeal perfusion), much more interest and more investigations are necessary to extend storage periods now measured in mere hours and days to the more optimum period of weeks and months.

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Proteinuria

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Guglielmo Salicetti,⁹⁰ about 1270, was the first to describe the association between renal disease and edema, but proteinuria was not discovered until Dekkers²⁸ of Leyden showed in 1673 that the urine of phthisical patients coagulated when acidified with acetic acid. In 1765, Cotugno²⁶ described coagulable urine in patients with dropsy, but its significance was not realized until Wells,^{105, 106} in 1806 and 1811, described kidney pathology associated with coagulable urine and dropsy. Wells thought that the substance in the urine was derived from blood. In 1836, Bright¹⁶ wrote that in some stages of renal disease, edema was associated with albumin in the urine, a milky serum, uremia, and occasional severe hypoalbuminemia. Sabatier,⁸⁹ referring to "Bright's disease" in 1834, suggested that the hypoalbuminemia was due to loss of albumin in the urine.

Since proteinuria has been recognized for three centuries, and its origin and importance have been known for over 150 years, I propose, in this review, to concentrate on the mechanism whereby proteins appear in the urine, and on the nature and significance of small degrees of proteinuria. The clinical importance and consequences of massive proteinuria (more than 0.1 gm. per kg. per day)³⁵ have been well reviewed in several articles,^{49, 85} and there is no longer any need to stress that patients with such massive proteinuria require full investigation, which should include renal biopsy. Much of our knowledge of the mechanism of proteinuria, however, has stemmed from studies on patients with massive proteinuria. Technical difficulties, resulting principally from the need for considerable concentration of urine samples, still obscure the exact process whereby proteins appear in the urine of normal people.

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THE MECHANISM OF GLOMERULAR PROTEIN FILTRATION

Dirks et al.,²⁹ using micropuncture techniques in dogs, found that the albumin concentration in the glomerular filtrate was usually less than 2.5 to 5 mg. per 100 ml. By immunofluorescent techniques,⁷⁸ Post showed that in physiological proteinuria, albumin and gamma globulin are both found in the proximal tubules in rats and adult humans. In normal humans, knowing the glomerular filtration rate, Jørgensen⁴⁸ estimated, by calculation, a mean normal glomerular filtrate total protein concentration of 8.6 ± 1.6 mg. per 100 ml., and Harrison et al.³⁹ calculated that for albumin, the normal filtrate/filtrand ratio was less than 0.03 per cent, giving a figure of about 1 to 2 mg. albumin per 100 ml. in the filtrate. One may estimate, then, that some 5 to 30 gm. of protein appear daily in the normal glomerular filtrate.

The exact mechanism of glomerular sieving of proteins is as yet unclear. In a series of elegant experiments in mice, using visual markers, Graham and Karnovsky³² showed by electron microscopy that horse-radish peroxidase (molecular weight 40,000) passed freely through the capillary wall into the glomerular space, whereas human myeloperoxidase (M.W. 170,000) was retained at the membrane between the epithelial cell foot processes, to be absorbed by the epithelial cells.

No pores across the capillary wall have been demonstrated, but it may well be that different layers of this wall act as barriers to different sized molecules. For example, Farquhar et al.³⁰ found the basement membrane itself to be responsible for holding up the passage of ferritin (M.W. 460,000) in rats.

Moreover, as Misra and Berman⁶⁹ have pointed out, it may be hard to rule out the presence of pores using two dimensional microscopy if the major component of basement membrane is a helical glycoprotein.

TUBULAR PROTEIN REABSORPTION

Once in the glomerular filtrate, the plasma proteins are, for the most part, reabsorbed—since the normal daily urine protein excretion is very roughly 1/100 of the amount in the filtrate. The evidence for this tubular reabsorption of proteins is overwhelming. Labelled proteins, injected into animals, appear in the tubular urine and, thereafter, in the luminal and later basal parts of the tubular cells (e.g., see Spector⁹³). Tubular protein reabsorption occurs in isolated nephrons,⁶⁰ and probably occurs by pinocytosis⁶¹ into intracytoplasmic bodies which experimentally contain the protein injected.⁷² Droplets form, their formation depending on tubular function in that they do not form unless tubular function is present, and their formation is inversely proportional to the rate at which the renal tubular cells catabolize the proteins. This catabolism, as well as water reabsorption, creates a concentration gradient between lumen and tubular cell, and this encourages further absorption. Although this renal catabolism is relatively unimportant as far as albu-

min metabolism is concerned,⁵⁰ it may be important in gamma globulin metabolism.⁹⁸

With the probable exception of the low molecular weight proteins (see below), tubular protein reabsorption is unselective. Thus, infusing albumin increases the clearance of globulins as well as albumin.³⁷ The nonselectivity of tubular protein reabsorption is further demonstrated by Harrison et al.,³⁹ who showed in patients with normal glomerular permeability to polymers (see below) that Bence-Jones proteinuria greatly enhanced the clearance of albumin and other proteins, by competition. In one fascinating case, a woman with 30 gm. Bence-Jones proteins per day and normal glomerular permeability, the albumin clearance was 0.03 per cent of the creatinine clearance, the maximum to which the albumin clearance can be raised by competitive failure of tubular reabsorption.

Tubular protein reabsorption is also Tm limited,⁵¹ though experiments involving infusion of macromolecules such as albumin are suspect because of glomerular changes due to plasma volume increases.^{58, 102}

In the nephrotic syndrome, the primary functional disturbance is an increased permeability of the glomerular capillaries to macromolecules.^{30, 33, 37, 44, 101} Tubular protein catabolism is increased^{46, 72} owing to the increased intraluminal protein concentration, but the tubular reabsorptive capacity for proteins is swamped, and all proteins sieved by the glomeruli then appear in the urine in relative amounts similar to those in the glomerular filtrate. It is probable that, at the same time, the peritubular capillaries become more permeable and that much protein is returned to blood via the renal lymphatics.²⁵

GLOMERULAR PERMEABILITY

With the development of immunological techniques⁹² which were both sensitive enough and at the same time proved the plasma origin of the proteins, it became possible to measure the renal clearance of plasma proteins, and, because of the unselectivity of tubular reabsorption, to draw conclusions concerning glomerular permeability from these clearances.

These clearances were first determined in patients with massive proteinuria, and they have proved a useful tool, provided that the urine has not been concentrated. Until very recently,⁷⁵ techniques for concentration caused variable and unpredictable loss of proteins, so that studies in which 50 to 1500-fold concentrations were often made^{6, 43, 76, 86, 87} must be accepted with caution.

In conditions of massive proteinuria in which glomeruli are diseased, there is excellent evidence for an inverse relationship between molecular weight and renal clearance,^{47, 62} and this relationship led to the concept of "selectivity."¹² Selectivity itself shows no correlation with the *amount* of proteinuria when this is above 1 gm. per day.

A direct proportion exists between the logarithm of the molecular

weight of a protein and its molecular size. The clearance of different plasma proteins may be related to one reference protein. Thus, in the clearance of IgG,

$$\text{IgG} = \frac{(\text{U. IgG}) \times v}{(\text{P. IgG})}$$

where U and P stand for urine and plasma concentrations, respectively, and v = urine flow in unit time.

If transferrin is the reference protein, the relative clearance of IgG as a percentage of that of transferrin (Rel. C. Tr.) = $\frac{\text{C. IgG}}{\text{C. Tr.}} \times 100$, and

since v cancels out, this becomes Rel. C. Tr. = $\frac{\text{U/P IgG}}{\text{U/P Tr.}} \times 100$.

Thus, one untimed specimen of urine may be used for protein clearance measurements.

The regression line (Figs. 1 and 2) relating the logarithm of the molecular weight to the logarithm of the relative clearance, is a description of the sieving characteristics of the altered, pathological basement membrane.¹⁹

After the initial reports,^{20, 43, 47} it became clear that this technique, though very crude, allowed the separation of patients with minimal change disease, who had a high degree of selectivity, losing large amounts of albumin but little of the large proteins into the urine, from other patients with membranous or proliferative glomerulonephritis. Since this separation was found to be important, in view of the difference in natural history and response to steroids, the measurement of selectivity became diagnostically, prognostically, and therapeutically useful.^{22, 23, 57, 100}

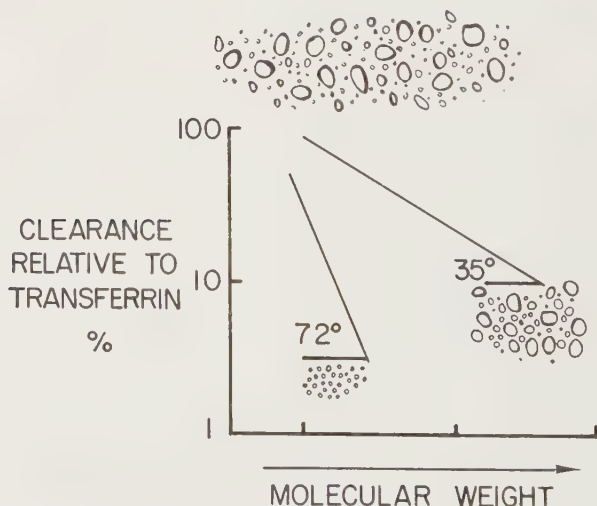


Figure 1. Differential protein clearances. Plasma, containing protein molecules of varying sizes, is sieved by the glomeruli in two different renal diseases. The pattern on the left is highly selective, only small molecules appearing in the urine. On the right, the pattern is unselective.

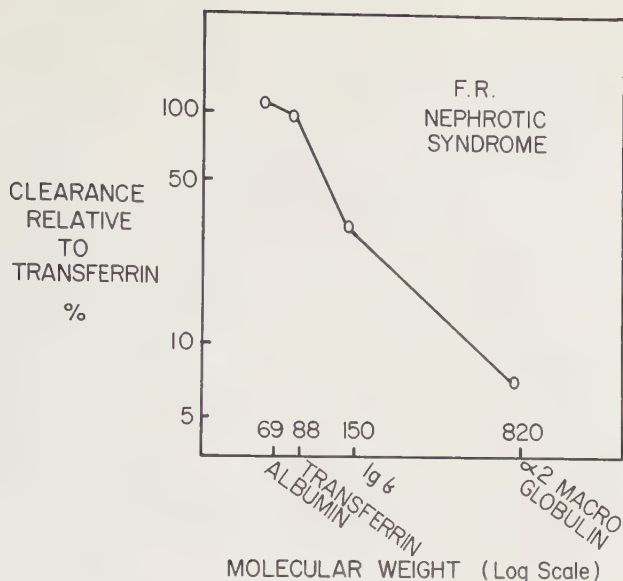


Figure 2. Relative clearances of four plasma proteins plotted against molecular weight ($\times 10^{-3}$).

Later, a simplified version, in which the clearances of only two proteins were compared, was developed by Cameron and Blandford,²² who used transferrin and IgG (M.W. 88,000 and 150,000, respectively), and by MacLean & Robson,⁶³ who used albumin and alpha-2-macroglobulin (M.W. 69,000 and 840,000 respectively).

These methods, while proving the immunological identity of the urine and plasma macromolecules, assume that the urinary proteins have the same molecular size as those in the plasma.

Hardwicke³⁴ and MacLean and Petrie⁶² showed that when the clearances of protein fractions of different molecular sizes were compared, there was very close agreement with immunological determinations of permeability using the same fractions.

Their method was to separate urine and plasma samples into 20 or 30 fractions on Sephadex G-200. Sephadex separates out proteins into successive collection tubes according to molecular size. Thus the slope of clearance of each fraction relative to tube number of the fraction (see Fig. 3) is another method of expressing glomerular permeability.

The closeness of agreement between the two methods suggests that in massive proteinuria, degraded but antigenically active protein fragments are uncommon; and the idea that protein clearances in *massive proteinuria* are meaningful is strongly supported.

Since endogenous proteins are of variable shape and charge, since they are readily reabsorbed, and since they may be degraded and, both in normal circumstances and in many renal diseases, are present in only very low concentrations in the urine, it would clearly be better to measure glomerular permeability using macromolecules that are inert, unchanged, and not handled by the renal tubules.

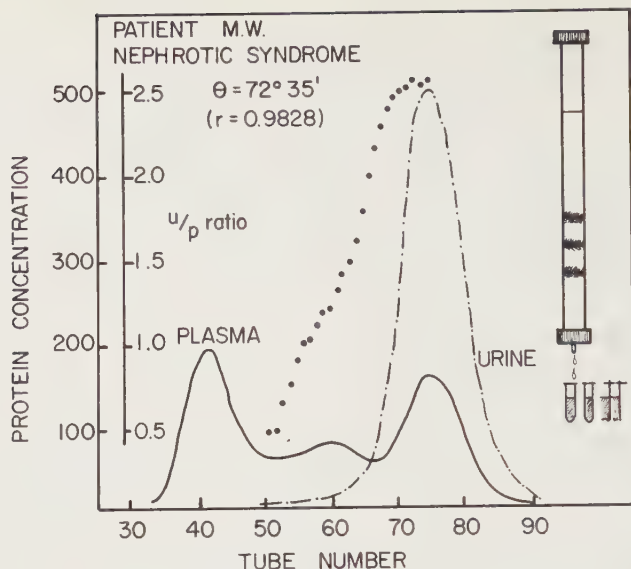


Figure 3. Protein clearances measured by Sephadex G-200 gel chromatography. The dots show the urine/plasma concentration ratios (U/P ratios) of each molecular size (tube number) fraction. θ = the "selectivity angle" or the tangent of the slope of relative clearance against molecular size. r = the linear correlation coefficient (Pearson).

Brewer¹⁵ found that dextrans of different molecular weights fulfilled these criteria, and Arturson and Wallenius⁵ described their use in humans, up to eight fractions being isolated. This technique, however, suffered from the disadvantage that so much dextran had to be infused that plasma volume increased—itself a cause of altered glomerular permeability.

Hulme and Hardwicke⁴⁴ got over this difficulty using radioactively labeled dextran and polyvinylpyrrolidone (PVP), the molecular size distribution of the polymer in urine and serum being determined by Sephadex G-200 filtration. In further papers,^{36, 45} the Birmingham group have shown with these techniques that there is indeed selective excretion of lower molecular size fractions and that there is a normal distribution of "effective pore size" in the filtration membrane, 20 or 30 fractions being measured (Fig. 4).

The influence of shape and charge of molecules is emphasized by the finding that, whereas albumin (with a molecular radius of 38 Å) has a clearance rarely above 2 to 5 per cent of the creatinine clearance, PVP of the same size had a clearance of 30 to 40 per cent of creatinine.³⁶

The use of labelled PVP has considerable advantages over that of proteins, since it is very reproducible, and since, with PVP, the whole range of permeability can be studied, whereas only the extreme upper range is investigated with proteins.⁴⁵ This has produced some expected findings (confirming, for example, selectivity estimates as measured by proteins), and also one very unexpected finding, that in some patients there is a reduction in glomerular permeability to molecules of less than 40 Å, including water and molecules of intermediate size, with none of

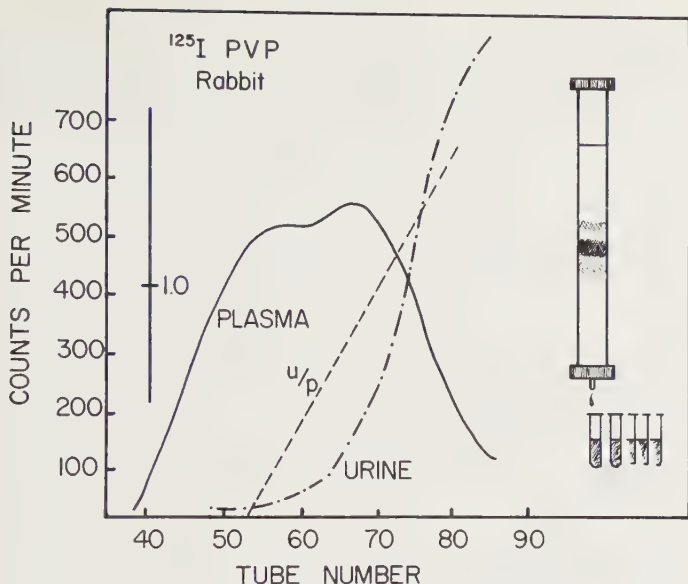


Figure 4. Urine/plasma concentration ratios (U/P ratios) of different molecular weight fractions (tube number) of radio-iodinated polyvinyl pyrrolidone (P.V.P.) in a rabbit, after Sephadex G-200 chromatography.

the normal sharp cut-off in the molecular sizes retained or excreted. (Polymers with molecular radii less than 24 Å are cleared as easily as creatinine, and those with radii greater than 60 Å are completely excluded from the urine.)

The agreement between polymer and protein estimates of permeability is best when glomerular lesions are uniform,⁶⁴ since the protein in the urine reflects only the behavior of glomeruli whose tubules have their protein reabsorptive capacity saturated.

What Clinical Usefulness Does the Concept of Selectivity Serve?

Clinically, the only reason for studying selectivity is to determine whether the patient's nephrotic syndrome is due to minimal change disease or not, the selectivity being high in this disease and, in general, low in other renal diseases.¹ Since minimal change disease (lipoid nephrosis) alone tends to respond excellently to steroids, and to have a good prognosis, and since not all children have minimal change, while some 18 per cent of adults⁸⁵ do have it, there is great need for such a test.²¹ Beyond making this important distinction, it is not possible to correlate the pathological lesion with the degree of selectivity, since the error in the protein studies is too great. Nevertheless, numerous such attempts have been made.^{12, 43, 47} Thus it is not possible to distinguish between membranous and proliferative glomerulonephritis from such studies.

Some recent experimental work is of great interest. Hawkins and Cochrane have shown that when glomerulonephritis was induced in rabbits using anti-rabbit glomerular basement membrane antibodies

raised in sheep, a polymorphonuclear leukocyte-mediated nephritis occurred with unselective proteinuria, possibly owing to basement membrane destruction by cathepsins D and E, or cationic proteins. Injury independent of polymorphs, however, produced a highly selective proteinuria, though in both cases the *amount* of proteinuria depended on the dose of antibody.

METHODS FOR MEASURING SELECTIVITY IN HEAVY PROTEINURIA

It has been shown that if two plasma proteins whose molecular weights differ quite widely are measured in plasma and urine, the relative clearances that can be measured compare well with methods using 5 to 7 proteins.^{22, 63} The absolute concentrations of proteins in plasma and a random urine sample are very conveniently measured by radial immunodiffusion on commercially available plates of agar impregnated with specific antiserum.⁶⁶

Although MacLean and Robson⁶³ have shown that the greatest accuracy is obtained with albumin and alpha-2-macroglobulin as the two proteins, there is usually (even in the nephrotic syndrome), so little of the latter that preliminary urine concentration is required, which introduces a tedious and potentially inaccurate step into the procedure. Neither transferrin nor IgG requires this step,²² but they are much closer together in size (M.W. 88,000 and 150,000 respectively) than albumin and alpha-2-macroglobulin (M.W. 69,000 and 820,000), which is an obvious disadvantage when making the clearance comparisons.

Two-protein selectivities may be expressed as the selectivity index or ratio of large protein clearance to small protein clearance. Using this technique, only 4 out of 30 patients with minimal change disease had selectivity indices above 0.2, whereas in severe proliferative glomerulonephritis only 3 out of 23 patients had selectivity indices below 0.2. When the index was below 0.04, 88 per cent of patients responded to steroids. When it was above 0.3, only 4 per cent responded.²³

MacLean and Robson⁶³ used a slightly more complex formula for their two-protein selectivities and found that in 48 adults with the nephrotic syndrome, the response rate to steroids was 78 per cent in the selective, and 4 per cent in the nonselective. Cameron²³ has commented that any test which can prospectively discriminate the response to treatment as well as this must be accounted useful. It must be stressed, however, that the use of protein selectivity tests in minor or physiological proteinuria has not yet been shown to be valid.

LOW MOLECULAR WEIGHT PROTEINURIA

There is, then, a linear and inverse relationship between molecular radius and clearance of the protein relative to creatinine.¹⁰ Albumin (molecular radius 36 Å) has a relative clearance almost equal to zero;

ovalbumin, at 29 Å, has a relative clearance of 23 per cent; myoglobin, 19.5 Å, has one of 75 per cent. For the 24 Å Bence-Jones monomer, the clearance is 40 per cent, but for the 30 Å dimer, the figure is only 4 per cent,³⁹ departures from linearity presumably being due to differences in charge and shape.

It is, therefore, not surprising that one finds proteins smaller than albumin and hemoglobin in the urine, both normally^{103, 104} and in renal disease. It is probable that these low molecular weight proteins normally pass into the glomerular filtrate and are for the most part rapidly reabsorbed, appearing in the urine in excess only when tubular reabsorption breaks down. When, at the same time, glomerular integrity is normal, as in specifically tubular dysfunction, such as that seen in the Fanconi syndromes or cadmium poisoning, a distinctive pattern of low molecular weight proteins will be found in the urine immunologically, electrophoretically, or by gel filtration.^{17, 38, 97}

Various proteins, including post gamma globulin,¹⁷ ribonucleases with M.W. 13,800 and 18,800,⁴¹ two proteins of 17 Å and 23 Å radii (M.W. 15,000 and 20,000 respectively)¹⁰ and lysozyme (muramidase),¹¹ are characteristically found in raised amounts in the urine in tubular disease. Lysozyme is perhaps the simplest to measure,⁷³ though its inappropriately low clearances suggest either protein-binding or dimerisation.⁴¹

Low molecular weight proteinuria has been found useful in the diagnosis of Fanconi syndromes and in renal transplant rejection, but not in the diagnosis of chronic pyelonephritis.³⁹ Their exact role is obscure.⁷¹ For example, excessive lysozyme concentrations in the blood cause other "tubular proteins" to appear in the urine, but massive large molecular weight proteinuria does not necessarily increase low molecular weight protein excretion rates.⁴⁰ It is therefore probable that the reabsorption of some low molecular weight proteins, in contrast to the larger proteins, is selective,⁴¹ as is the case with tubular amino acid reabsorption.

Low molecular weight proteins will appear in the urine in any condition in which there are excessive quantities of these proteins appearing in the blood. The first of these conditions to be reported was myeloma with Bence-Jones protein in the urine.⁷ Bence-Jones protein is characteristically precipitated in weakly acidic solution at 45 to 60° C, and it usually, but not always, becomes soluble on boiling. Immuno-electrophoretic methods for Bence-Jones protein are far superior.^{36, 70} Such paraproteins do not cause positive Albustix tests.⁸¹

There are two main groups: a monomer (M.W. 22,000) and a dimer (M.W. 44,000)³⁹ with appropriate clearances (see above). Because of the rapid clearance, detectable levels in the blood are rare, unless polymerization of light chains occurs so that glomerular sieving is prevented.¹⁸

A complicating feature is that, whereas proteinuria occurs in 70 to 80 per cent of myeloma and a third of cases of Waldenström's disease, in only about half is the proteinuria due to Bence-Jones protein. Glomerular changes occur in myeloma,³¹ macroglobulinemia,⁴ and cryoglobulinemia,⁷⁷ and since the Fanconi syndrome also occurs in these conditions, any proteinuria may have several causes.

The same is true, for example, of the excessive lysozymuria that occurs in monocytic and myelomonocytic leukemia, in which there is increased release of lysozyme into the circulation,^{71, 73} and in which the occurrence of glycosuria, excessive potassium loss, and poor titratable acid excretion provide evidence of marked tubular dysfunction. There are now reports of patients with disseminated neoplastic disease excreting peptides and occasionally proteins (M.W. 12,000 to 50,000) into the urine.⁸⁸ While this is not yet of diagnostic help, Wiernik and Serpick¹⁰⁷ feel that serial serum and urine lysozyme levels are, in acute monocytic leukemia, helpful prognostically, and are at least as valuable as serial bone marrow assays in clinical assessment.

SOME OTHER PROTEINS FOUND IN THE URINE

Tamm-Horsfall Protein^{67, 94}

This mucoprotein is derived from the urinary tract, not from the serum. Its predominant form consists of four molecules, each of M.W. 7 million, joined together into a rod some 12,000 Å long. It constitutes some 70 per cent of the nonserum proteins; is excreted in amounts of 10 to 140 mg. per day and is precipitated by 0.58 molar NaCl. Immunological studies have shown it to be an important constituent of urinary casts.⁶⁵ It depolymerizes into smaller molecules moving with the alpha-1-globulins.

Fibrinogen Split Products

Fibrinogen fragments, particularly E, have been found in the urine in a variety of renal disease,⁸⁰ and D and E have been found during episodes of renal graft rejection,¹⁴ disappearing with intensified immunosuppression. Antoine et al.² found a correlation between fibrinuria following transplantation, and a nonselective pattern of urinary serum protein loss, the fibrinuria correlating with the development of late kidney lesions. Ischemia, intravascular fibrinolysis, microthrombi, and antibody-antigen reactions have been proposed as causes. The importance of fibrinuria in acute renal failure, as a diagnostic or therapeutic guide, is under investigation.

Complement

Laguerre et al.⁵³ found C-1, C-2, C-3, and C-4 complement in the urine of nine of 24 patients with various renal diseases, depending on the immunological lesion and not on the occurrence of proteinuria. It not yet known whether this will be useful clinically.

Enzymes

One might expect that enzymes would be particularly useful substances to measure in the urine. They are proteins of widely differing molecular weights and, partly because of this, have been used for experimental studies of glomerular filtration.³² Since lysozyme (muramidase) and ribonuclease are relatively small, both have been used to study low

molecular weight proteinuria due to failure of tubular reabsorption. Blainey¹³ has shown that the clearances of ribonuclease, amylase, and malic dehydrogenase are appropriate to their respective molecular radii.

In addition, one would expect that any enzymes of small enough molecular size would, if liberated into the blood stream in excess, appear in the urine. Urinary amylase, lipase, and pepsinogen have been particularly useful diagnostically in pancreatic and intestinal disease.

Finally, one would anticipate that the kidney itself, if damaged, would liberate enzymes into the urine owing to cell death and to increased membrane permeability, offering diagnostic help similar to that given by serum enzymes in heart and liver disease. This whole subject has been reviewed by Mattenheimer.⁵⁹

Kidney cell damage causes an increase in enzymes, some 30 of which, together with inhibitors, have been described.⁷⁹ There tends to be an increase in enzymes proportional to their concentration in the various tissues of the kidney. Thus, since the first isoenzyme of lactic dehydrogenase is the predominant cortical isoenzyme, it is the predominant one in the urine, and though various lactic dehydrogenase isoenzyme patterns are characteristic of different renal structures, no urinary isoenzyme pattern is typical of renal disease.

Raised urinary amino transferase, leucine aminopeptidase, beta glucuronidase, and alkaline phosphatase levels have all been found in renal disease, but other tissues (such as leukocytes and red cells) contain enzymes, and even when it is established that the enzymes are due to renal damage (of any sort), all that this indicates is that something is wrong with the kidney. Urinary enzymes are useless in the differential diagnosis of renal disease.^{59, 108}

NORMAL PROTEINURIA

Polymer studies have shown that the normal glomerulus is extremely selective,^{45, 64} but this is not what is found when *protein* selectivity studies are done on normal people.⁷⁶ Moreover, the low molecular weight proteins in normal urine differ from those in tubular proteinuria,³⁸ suggesting that their appearance is not due to failure of tubular reabsorption. Thus a beta protein of 19 Å size and two gamma proteins of 16 Å size are found, neither of which is typical of tubular disease.

Perhaps the greatest difficulty is the small quantity of proteins normally excreted, which inevitably means that considerable preliminary concentration of urine must be done,^{8, 76, 86} with substantial loss of proteins in the process (for example, 80 per cent of the albumin in one study⁸⁶).

Berggård et al.⁹ found 23 constituents of normal plasma in normal human urine and eight low molecular weight proteins have been found.⁷⁴ Macromolecules larger than M.W. 200,000 are not found in normal urine (e.g., fibrinogen, IgM, IgD), but IgE, with M.W. 200,000 is found,⁹⁹ and secretory IgA, sedimenting at 10.9 S, is also found.¹¹

Turner et al.,⁹⁹ finding that the clearance of IgE is about 100 times

greater than that of albumin, calculate that local production accounts for almost all of the urinary IgE, and the same may be true for secretory IgA.

The extent of normal proteinuria reported varies with the analytical methods used as well as with the length of urine collections and the control of posture and exercise. From Table 1 it can be seen that a daily protein excretion rate below 150 mg. per 24 hours is probably normal. The excretion rates show no relation with age.^{48, 96}

Using a radioimmunoassay method, Keen and Chlouverakis,⁵¹ measuring recumbent 2-hour albumin excretion rates, showed that the normal curve was J-shaped, more than half their normals having urine albumin concentrations below 1 mg. per 100 ml., and 90 per cent excreting less than 2.6 mg. of albumin in 2 hours. These rates are increased some 10-fold on standing.⁸³

Using much cruder methods, Theil et al.⁹⁵ found an incidence of proteinuria (more than 1+ on dipstick test) in 991 students aged 14 to 19 years to be 5.2 per cent, similar to the figure of 1 to 5 per cent found by Bernard et al.¹⁰ in a review of published reports of proteinuria in young servicemen.

Postural and Exercise Proteinuria

In some individuals (some 3 to 5 per cent of healthy adolescents and young adults), orthostasis or lordosis may cause such an increase in proteinuria that it is detectable by crude clinical methods, and in renal disease, already abnormal mild proteinuria is increased by standing upright.⁵² Rowe and Soothill⁸⁷ showed a poorly selective proteinuria, but dextran selectivity was very high,⁶⁴ suggesting that in postural proteinuria there is no change in glomerular permeability. These last-named authors feel that this, together with low protein selectivity, suggests that the proteins originate from the renal lymphatics, lymph formation being unselective.⁹¹

Table 1. Normal Urine Protein Excretion Rates

AUTHOR	MEAN 24 HOUR URINE TOTAL PROTEIN	
Rigas and Heller ⁸² (1951)	39.0±5.7 mg. per 24 hours	albumin 14.8±2.2; globulin 25.8±3.9
Webb, et al. ¹⁰³ (1958)	133 mg. per 24 hours	23% albumin
Melo, et al. ⁶⁸ (1959)	126.3 mg. per 24 hours (range 90.5 to 167.8)	
Jørgensen ⁴⁸ (1967)	118.7±18.5 mg. per 24 hours per 1.73 m ²	males 122.3±16.8; females 115.3±19.8

Once more, the proteins have to be measured after massive concentration of the urine, so that the poor correlation between molecular weight and clearance, both in postural proteinuria and in the proteinuria that follows exercise,^{27, 76, 87} may be an artefact.

Exercise, depending on its severity, may increase proteinuria some 50-fold, owing to loss of plasma proteins into the urine, and the increase is not due to low molecular weight proteins. Castenfors et al.²⁴ conclude that during exercise, glomerular permeability to albumin is increased. Thus the mechanism in the two forms of proteinuria may not be the same.

When is Proteinuria Excessive and What Does it Imply?

Because of the generally very poor correlation between renal histological changes and the changes in protein excretion, we are left with a situation in which renal disease, sometimes very severe, may exist without clinical proteinuria (for example, some cases of chronic renal failure and polycystic disease), and, at the other extreme, with massive proteinuria but no other histological change except a reversible fusion of the epithelial foot processes, observed on electron microscopy ("minimal change disease" or "lipoid nephrosis").

The whole subject is made harder because of the different methods used to register proteinuria clinically. Few people now acidify urine and boil it or use sulfasalicylic acid. For more than 10 years, test tapes (e.g., Albustix), which depend upon the protein error of indicators, have been used almost universally. They give accurate, reproducible results, observer variation being negligible.⁸¹ A negative albustix test indicates a urinary protein concentration below 4 mg. per 100 ml. A "trace" reading indicates a protein concentration in the ranges of 1 to 30 mg. per 100 ml. A reading of 2+ strongly indicates significant proteinuria. A reading of 1+ is somewhat equivocal, and another urine specimen should be checked. Albustix test tapes have the additional advantage that they do not give false positive reactions with radiopaque materials or tolbutamide, unlike sulfasalicylic acid.

Since posture, build, exercise, and the state of diuresis will all influence the urine protein concentration, which is what is being measured, the finding of protein on a dipstick test must be followed up by more controlled studies. The urine must first be examined microscopically.

Assuming that no other urinary abnormality is found, a specimen must be obtained that has been passed when the subject, who has emptied his bladder on retiring the previous evening, gets up in the morning. If there is protein or any other abnormality in such early morning specimens, one or preferably two 24 hour urine collections should be made for total protein estimation (sulfasalicylic acid). If this is below 100 to 150 mg. and no other clinical or urinary abnormality has been found, then no further investigation is required.

If there are other abnormalities, or if protein excretion is persistently raised, further investigation, including renal biopsy, should be considered. Such investigation may be required not merely to satisfy patient and doctor, but also because jobs and insurance may depend upon their being done.

It must be stressed that measurement of proteinuria is an adjunct to, and does not replace, microscopy of the urinary sediment, bacteriological examination, measurement of creatinine clearance, and excretory pyelography.

The clinical problem of the apparently healthy patient with proteinuria who has no evidence of systemic disease such as hypertension or diabetes mellitus, and no other evidence of renal disease such as an abnormal urine sediment or excretory pyelogram, has not yet been resolved.

The outlook in these patients is, however, becoming clearer, principally through the work of Antoine² and his group in France, and Robinson and his co-workers at Duke University.⁵⁵

Robinson, in his excellent review of this subject,⁸⁴ notes that in various studies either posture has been uncontrolled and proteinuria called either (a) "persistent" or (b) "intermittent," or posture has been controlled and proteinuria called (c) "constant" (proteinuria present when recumbent as well as during quiet upright ambulation), (d) "fixed orthostatic," (proteinuria always present only when upright), or (e) "transiently orthostatic" (occasional proteinuria in the upright position only).

Renal biopsy studies have shown a high incidence (60 to 80 per cent) of definite pathological changes in (a), (b), and (c), and a low incidence in (d). No such studies have been done in (e). There are also "subtle architectural alterations, usually glomerular in nature which have been felt to be abnormal but not sufficiently so to justify a pathologic diagnosis," occurring in all groups, but in 45 per cent of group (d).⁸⁴ No pathological or architectural alteration is specific to any group, and the architectural changes may well have no practical significance.

The short term prognosis (up to 5 years) in "fixed, reproducible orthostatic proteinuria" is excellent in all studies, either because the pathological process has stopped, or its progression is so exceedingly slow. Even with definite renal pathology, Antoine et al.³ found functional impairment developing in only two of 16 patients, and after more than 15 years of proteinuria. If hematuria develops, however, the prognosis becomes much worse.

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Clinical Testing of Renal Function

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PHYSIOLOGICAL CONSIDERATIONS

The kidney maintains a constant internal environment by removing metabolites and controlling the loss of various body substances. This is achieved by filtration at the glomerulus, selective reabsorption by tubular cells, and secretion of unwanted substances into the tubular lumen.

The structure of the kidney is highly adapted to perform these functions. Two million glomeruli provide a capillary surface area of 1 square meter. The glomerular capillaries, unlike other capillaries, are bound proximally by afferent and distally by efferent arterioles, and are invested with vascular endothelium and capsular epithelium. The glomerular capillaries are concerned only with filtration, and the capillary pressure here is twice that of capillaries elsewhere. These properties allow auto-regulation of the glomerular filtration rate (GFR).

The macula densa consists of a group of tall, narrow cells in the pars recta of the distal tubule near the glomerulus. It acts as a chemoreceptor for electrolyte excretion, particularly sodium, and it assists in maintaining glomerulotubular balance and autoregulation of the glomerular filtration rate. The loop of Henle and vasa recta are adapted for counter-current multiplication to maintain a hyperosmolar medulla and concentrate the urine. The juxtamedullary nephrons constitute 14 per cent of the nephrons. They have long loops of Henle which extend into the inner medullary zone and renal papilla and are responsible for achieving maximum concentration in man.¹²

Blood received by the kidneys constitutes about 20 per cent of the cardiac output. The renal plasma flow is 650 ml. per minute, and 130 ml. of protein-free filtrate is formed in the glomeruli each minute. During the passage of the filtrate through the proximal tubule, glucose and bicarbonate are reabsorbed in toto. About 80 per cent of sodium and water are reabsorbed. Further reabsorption of sodium takes place in the distal tubule. Water reabsorption in the distal tubule and collecting

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duct is controlled by antidiuretic hormone and the countercurrent system of the loop of Henle and vasa recta. Some of the filtered urea is reabsorbed, the reabsorbed amount being increased when the urine flow is decreased. Creatinine is added to the filtrate by secretion. Potassium is secreted in the distal tubule in exchange for sodium. Along the entire tubule, hydrogen ions of tubular cells are exchanged for sodium ions of tubular fluid. Hydrogen ions are excreted as titratable acid and ammonium.

In 24 hours, about 1500 ml. of urine is normally formed. This contains 15 to 25 gm. of urea, 1 to 1.5 gm. of creatinine, 700 to 800 mg. of uric acid, 50 to 60 mEq. of hydrogen ions, 50 to 60 mEq. of potassium, and 80 to 100 mEq. of sodium. Since many factors control the excretion of these substances, their mere measurement would be insufficient to assess renal function. Normal kidneys are able to function with extraordinary flexibility and are able to maintain a constant internal environment despite extremes of fluid and electrolyte insults. For the kidneys to function normally, it is essential that the renal blood flow is normal, the nephrons are intact, and various enzymes and hormones are present. As renal function deteriorates, this normal flexibility is gradually reduced.

GENERAL PRINCIPLES OF RENAL FUNCTION TESTING

Renal function tests are done when renal disease is suspected clinically and when the urine is abnormal. The tests supplement the impression obtained from the history and physical examination, and are used for evaluating the clinical course of the disease as well as for diagnosis. Serial tests, of particular value in assessing the efficacy of treatment, are also of value when nephrotoxic antibiotics are used and when kidney function is assessed after renal transplantation. In the clinical testing of renal function, simple, rapid methods that are consistently reproducible are more important than accurate measurements requiring meticulous care. No simple test can measure renal function with any degree of accuracy or consistency, and an overall picture is best obtained by combining a number of clinical tests.

Great care should be exercised in the collection of urine specimens. Clean-voided specimens are desirable. If the urine is cloudy it should be filtered. Fresh specimens should be used for all tests. For determination of clearance rates, accurately timed specimens are mandatory. The bladder should be completely emptied. The urine should be collected in a transparent utensil so that macroscopic abnormalities can be observed, and the specimen should be accurately measured in transparent measuring cylinders. All utensils should be clean and dry. For routine clinical tests catheter specimens are not necessary. The more refined tests of renal function must be done under basal conditions, and where appropriate, the results should be interpreted in relation to age, sex, and surface area of the body.

In this review the commonly performed clinical tests will be discussed, with emphasis on recent progress and clinical application of these tests.

RENAL CONCENTRATION TEST

Renal concentration was one of the earliest tests used to evaluate renal function. It is still widely used, but poor instrumentation and misinterpretation of results requires that its use be further elaborated.

The ability of the kidneys to concentrate the urine—up to 4 to 5 times that of blood—provides an extraordinary mechanism for conserving water without compromising elimination of the waste products of metabolism. This concentrating ability is lost early in renal disease. When damage to the medulla is disproportionately greater than that to the cortex, there is greater loss of concentration, in comparison to other tests of renal function.

The concentration of urine is ordinarily measured by its specific gravity, determined with a clinical hydrometer. This method frequently gives inaccurate results for several reasons.³⁸ A relatively large volume of urine is necessary, and if the amount is inadequate, the specific gravity determination is of little value. Use of a narrow cylinder which closely hugs the hydrometer also gives inaccurate results. An unclean instrument is also a common cause of inaccuracy, as is neglect of temperature adjustment.

Misinterpretation of results is mainly a result of equating normal concentration of urine with normal renal function, and loss of concentrating ability with abnormal renal function. It is thus preferable to use the concentration test along with other tests of renal function in assessing the overall function of the kidney.

The most reliable measure of concentration is the osmolality of the urine. Osmolality refers to the number of osmoles of a solute per kilogram of solvent (water). It is determined by measuring the freezing point of urine and then reading the appropriate value from conversion tables.³⁸ Although this measurement is accurate and precise, the instrument required is expensive and therefore not generally available.

The refractive index of urine can be measured with a temperature-compensated hand refractometer. This is highly recommended for its rapidity, simplicity, compactness, low cost, and the small sample of urine required.^{31, 39} The total solids (TS) meter is also a temperature-compensated hand refractometer. However, the refractive index is converted to specific gravity, which is a less accurate measure than the actual refractive index. The instrument has two scales, one of which measures the total solids and water content, and the other the specific gravity. When a drop of urine is placed in the instrument a line between dark and light fields crosses the scale at the point of reading. The hand refractometer and TS meter are both choice instruments for clinical use.

Before embarking on a formal concentration test, it is useful to meas-

ure the concentration of several random specimens of urine. This has several advantages. If the urine concentration is within the normal range, no further test is necessary. A high degree of concentration may indicate the presence of sugar or contrast media. When measuring protein qualitatively, it is useful to know if the urine is diluted or concentrated. In a concentration test, appropriate adjustments must be made when there is protein and sugar in the urine.³⁹ Although maximum concentration of urine can only be achieved with prolonged hydropenia, lasting 24 to 36 hours,²⁹ it is not necessary to subject all patients to this uncomfortable procedure.

Procedure. A dry supper is prescribed, and after 6 P.M. the patient fasts until 10 o'clock the next morning. This period of fasting may be prolonged as necessary.

All urine samples are collected separately. The sample obtained during the last hour of the test is usually the most concentrated. The concentration of each specimen is measured, and the highest reading is recorded. The normal range for osmolality is 800 to 1400 mOsm. per kg. of water; for the refractive index it is 76 to 140, and for specific gravity it is 1.022 to 1.035.

While patients with normal and abnormal concentration can usually be quite easily separated, there will be a group with boundary values.³⁹ In these patients the decision to prolong the period of water deprivation will depend upon the clinical state of the patient, the clinical diagnosis, and the importance of the test in the clinical setting.

Maximum concentration of urine may not be achieved if there has been a high fluid intake prior to the test³⁶ or if there is diuresis of edema fluid. A high-protein diet augments the concentration of urine, whereas a low-protein diet and salt restriction tend to give lower values.

The clinical value of the concentration test lies in its ability to detect early defects in renal function. For instance, decreased concentration in essential hypertension and diabetes mellitus may occur much before any alteration in the other renal function tests is seen or renal disease is suspected clinically. Persistent failure to concentrate the urine despite a relatively good glomerular filtration rate may be the result of tubular disease due to severe potassium deficiency and the Fanconi syndrome, tubular resistance to antidiuretic hormone as seen in nephrogenic diabetes insipidus and hypercalcemia, damage to the juxtamedullary glomeruli as in sickle cell trait, and disease or disturbance of the counter-current multiplier system which occurs in interstitial nephritis, chronic pyelonephritis, polycystic disease of the kidneys, and hydronephrosis.

In patients in acute renal failure, determination of the concentration of urine may be of help in differentiating renal from prerenal failure. In renal failure the urine osmolality is low, whereas in prerenal failure it is high. If the ratio of urine osmolality to plasma osmolality is less than 1.35, renal failure is most likely. In patients with upper urinary tract infection, there is usually a defect in the concentration of the urine, whereas with lower urinary tract infection, the concentrating ability is normal. When the upper urinary tract infection is eradicated, renal concentration may return to normal. In women with asymptomatic bac-

teriuuria of pregnancy, it has been shown that as pregnancy advances, the concentration of the urine tends to decrease. Associated with this is a high incidence of acute pyelonephritis, and this is much more difficult to treat in such patients than in those whose concentration defect is not so severe.³⁷

The concentration test is not of much value in chronic renal disease. Indeed, it is not without some considerable risks, particularly when prolonged dehydration is employed. The patient's condition may deteriorate and acute renal failure may be precipitated. In patients with urinary infection, obstruction of the urinary tract may occur. If, for any reason, hydropenia is not tolerated by the patient or is likely to lead to some complications, pitressin tannate in oil may be used, 10 mg. given intramuscularly. All urine specimens over the next 24 hours are then used for measuring the concentration. This drug must be used cautiously in patients with chronic renal disease, since retention of fluid to dangerous levels may occur. However, it has been found that the concentration of urine by this procedure is usually slightly less than that following hydropenia.³⁵

THE PHENOLSULFONPHTHALEIN EXCRETION TEST (PSP TEST)

This test was first described by Rowntree and Geraghty in 1910.³³ It has enjoyed a long period of usefulness and is still commonly done in many parts of the world. Because of its lack of precision, however, it has been supplanted by other tests of renal function. Since 94 per cent of the dye is excreted through the tubules and only 6 per cent by glomerular filtration,¹⁹ it is essentially a test to measure renal blood flow (RBF), and only indirectly reflects changes in the GFR. Reduced excretion of dye may be due to decreased RBF, decreased GFR, or obstructive uropathy. Delay in excretion of dye is indicative of a reduced GFR or obstructive uropathy. The dye is secreted entirely by the proximal tubule, but with 6 mg. dose the plasma level is not sufficiently high to saturate the tubular capacity to excrete phenolsulfonphthalein. Tubular excretory capacity cannot be measured until the plasma level reaches 1 mg. per 100 ml.

Measurement of the excretion of dye in the first 15 minutes gives the most accurate and reliable results. At 2 hours, normal values may be obtained despite poor renal function. This is probably related to repeated recirculation of dye.³² Opinion is divided regarding the desirability of giving fluids before the test. It tends to increase the excretion of dye in patients with good renal function. In patients with poor renal function diuresis is delayed and dye excretion may be increased in the diuretic phase. In order to standardize the test, it is advisable to prohibit fluid intake before or during the procedure. The accuracy of the test is enhanced when there is relative oliguria.

One of the great drawbacks of the PSP excretion test is the difficulty in collecting the proper urine samples. Even normal subjects experience

difficulty in voiding on time. Patients with atonic bladders or prostatic obstruction have variable amounts of residual urine, and the test becomes meaningless when the bladder is not emptied completely. Accordingly, patients must be carefully selected for the test. Catheterization should be avoided. To facilitate voiding on time, the patient is advised not to empty the bladder during the hour preceding the test.

Other factors may invalidate the test. In patients with liver disease, PSP excretion is increased because of failure of the liver to eliminate the dye in bile.²⁰ Excretion of the dye is 10 to 13 per cent greater when the patient is in the supine rather than the erect position.⁶ Because of competitive inhibition, PSP excretion is reduced by penicillin, sulfonamide, salicylates, diuretics³⁴ and high uric acid. The test is also invalidated in patients with low serum albumin levels and in those with multiple myeloma. In the elderly and in patients in heart failure, dye excretion is reduced.

Procedure. The test is done with the patient lying quietly in bed. Six mg. of phenolsulfonphthalein is rapidly given intravenously. Extravasation of dye into tissues should be avoided. The time of injection is recorded, and exactly 15 minutes later the patient is instructed to void. The bladder should be emptied completely. The urine is made alkaline with the addition of 10 per cent sodium hydroxide to bring out the red color. The volume is then made up to a liter with distilled water. The mixture is then compared colorimetrically with a standard solution. With normal renal function, 25 to 50 per cent of the dye is usually excreted in 15 minutes. As renal function deteriorates, less dye is excreted; in the final stages of deterioration, no dye appears in the urine in the first 15 minutes.

In an effort to improve the accuracy of the standard PSP excretion test, several modifications have been introduced. In one method, 18 mg. PSP per square meter of body surface area was given intravenously.²² The 15 minute urinary excretion of dye correlated well with plasma creatinine level. In another modification, 1 mg. PSP per kg. of body weight was given intravenously, and rate of fall of concentration of dye in plasma at 5 minute intervals from 15 to 35 minutes was plotted.¹⁶ The rate of fall correlated well with the urinary excretion of dye at 15 minutes, and creatinine, inulin, and PAH clearances. This test is of advantage in patients with residual urine or with urinary drainage into bowel or fistulae.^{17, 18} The disadvantage is the extra time needed for estimating the plasma level of dye. Workers in Germany found that the plasma concentration of PSP 60 minutes after injection of 60 mg. intravenously correlated well with creatinine clearance.²³

PSP can also be used to estimate residual urine volume.² A diaper PSP test has been used to diagnose congenital renal disease in the neonate.³

BLOOD UREA NITROGEN

This is probably the most widely used test of renal function. The normal range for the BUN is 10 to 20 mg. per 100 ml. In a steady state,

the BUN is dependent on production and elimination of urea by the kidneys. In this state it might be assumed that the BUN is a good measure of renal excretory function. In practice, it turns out that the BUN may be within normal limits despite a reduction of the GFR by more than 50 per cent. It is therefore not a good test of renal function in the early stages of renal insufficiency. The BUN is dependent on the state of hydration, the circulation, and the rate of urine flow, and is higher in states of hydropenia.

Several factors may alter the BUN while renal function remains unchanged. It is high in normal subjects with high protein intake.¹ Endogenous protein catabolism associated with severe trauma, infection, fever, and steroid treatment results in elevated levels of the BUN. Absorption of blood from the upper gastrointestinal tract will result in a rapid rise of the BUN. The anti-anabolic effect of tetracycline will cause a rise in patients with renal insufficiency.⁴ The BUN is low in pregnancy, in patients on a low protein diet, and in those with liver disease.

While many factors tend to limit the usefulness of the BUN as an index of renal function, it is still of value, provided that it is interpreted in the proper perspective. It also has clinical value. An unexpectedly high BUN level may point to occult upper gastrointestinal bleeding. Frequent BUN determinations are needed if tetracycline is the only antibiotic to which an organism is sensitive in a patient with renal failure. In such a situation minimum effective dose should be used and BUN should be done at frequent intervals. Should there be clinical deterioration associated with a progressive rise in BUN, tetracycline should be withdrawn.¹¹

SERUM CREATININE

Serum creatinine determination is a useful measure of nitrogen retention in renal insufficiency. Its main drawback is related to the non-creatinine chromogens which are measured when the Jaffe picric acid method is employed.⁵ However, true creatinine could be estimated by absorbing noncreatinine chromogens on Fuller's earth,²¹ or an enzymatic method could be employed.²⁷ In patients with renal disease, the variability for true creatinine is no greater than for chromogen creatinine.⁸

Creatinine production is related to muscle mass, and the serum creatinine is thus slightly higher in males than females. The amount of creatinine excretion in adolescence is also related to age and sex.⁴⁰ In normal subjects the amount of creatinine excreted is dependent on active muscle mass, and it may be altered in certain diseases and during exercise. In any individual, creatinine excretion tends to vary from day to day and this may be due to variation in its production or secretion.¹⁰

Since serum creatinine is not altered appreciably by exogenous factors it is a better measure of renal function than the BUN. However, like the BUN, its value is limited in early renal failure, when marked reduction of the GFR may be associated with little change in serum creatinine. It is more useful in chronic renal failure, and is particularly valuable in following the progress of the disorder. Simultaneous meas-

urement of the BUN and creatinine levels offers more information. Usually the BUN level is about 10 times greater than the serum creatinine level. A lower ratio is associated with severe disease and a low protein diet. A higher ratio reflects excessive nitrogen intake, hypercatabolic state, upper gastrointestinal hemorrhage, and acute renal failure.

SERUM URIC ACID

The normal range of serum uric acid is so wide¹³ that it cannot be used routinely as a test of renal function. The rise in uric acid in renal failure is also inconstant. In some instances it may be elevated before serum urea,²⁸ whereas at other times it may be normal despite a marked reduction of glomerular filtration rate.²⁴ In early stages of renal failure, the rise in serum uric acid usually parallels the rise in serum urea. With progressive azotemia, the rise is less than that of serum urea, and terminally the level may actually drop. In patients with gout or familial hyperuricemia there is a selective defect in uric acid excretion as well as increased production of uric acid. Raised plasma lactic acid is known to impair uric acid excretion, and this may be the mechanism for hyperuricemia in essential hypertension,¹⁴ toxemia of pregnancy,⁷ myxedema, glycogen storage disease, alcohol intake, and ketosis. Direct inhibition of tubular secretion of uric acid is produced by pyrazinamide, pempidine, mecamlamine and diuretic agents. Clinically, unusually high plasma uric acid levels may suggest gouty nephropathy, myeloproliferative disorders, or lead nephropathy.

UREA AND ENDOGENOUS CREATININE CLEARANCES

The clearance of a substance denotes the amount of blood that is completely cleared of the substance in a unit of time. The volume is identical with the glomerular filtrate if the substance is freely filterable at the glomerulus, and is neither reabsorbed nor secreted through the tubules. The volume is only theoretical, since the substance is not completely removed in a single circulation through the glomerulus. Nevertheless, this clearance measures the GFR. Unfortunately, there is no substance normally present in the blood which fulfills the criteria. Inulin, a non-metabolizable carbohydrate, meets the requirements and is widely used to measure the GFR. However, since it involves constant infusion at a precise rate and accurate timing of blood and urine samples, it is not a satisfactory method for routine clinical testing.

While urea is freely filtered at the glomerulus, some of it is reabsorbed by the tubules, the amount reabsorbed being dependent on urine flow. At urine flow rates above 2 ml. per minute, urea excretion is relatively constant. Although urea clearance has been used as a measure of GFR for a long time, its popularity has diminished with the introduction of other methods of measuring GFR. Many factors contribute to making urea clearance an inaccurate measure of GFR. These are the numerous

exogenous factors determining the level of serum urea, reabsorption of urea by tubules, and dependence of urea excretion on rate of urine flow. Creatinine is also freely filtered at the glomerulus, but some is also secreted by the tubules. Unlike urea, however, creatinine excretion is not dependent on urine flow. Because there are fewer variables with creatinine, endogenous creatinine clearance is more accurate than urea clearance. While it is customary to do a 24 hour creatinine clearance, difficulties associated with 24 hour urine collections militate against accurate clearance. The relatively constant excretion of creatinine in an individual throughout a 24 hour period lends itself to clearances over short periods.

PROCEDURE FOR CLEARANCE STUDIES

Early morning is the most suitable time for this study. The subject is advised to take several glasses of water before and during the test period to ensure a urine volume of greater than 2 ml. per minute. At the beginning of the test the subject voids and the urine is discarded. He then lies quietly in bed until termination of the test. Urine collections are made at the end of 1 hour and again at the end of another hour. Blood samples are drawn at the midpoints of the first and second urine collections. Complete emptying of the bladder is mandatory. Bladder catheterization for this procedure is unwarranted. The test is invalidated in patients with large residual volumes. The urine volumes are accurately measured, and samples of urine and blood are sent to the laboratory for urea and creatinine estimations. The duplicate test acts as a convenient check. Urea clearance is then calculated by taking the product of the urea concentration in the urine in mg. per ml. and the urine volume in ml. per minute, and dividing by the serum urea in mg. per ml. Endogenous creatinine clearance is calculated in the same way. The clearance is expressed in millimeters per minute. The final clearance is then expressed in relation to the surface area of the body.

The normal urea clearance is 75 ml. per minute, which is 60 per cent of the inulin clearance. With impaired renal function, the ratio of urea clearance to inulin clearance is higher, amounting to as much as 90 per cent. The endogenous creatinine clearance is 97 to 140 ml. per minute in men and 85 to 125 ml. per minute in women.⁹ The ratio of creatinine clearance to inulin clearance is highest when the GFR is from 20 to 80 ml. per minute. When the GFR is below 15 ml. per minute, the ratio of creatinine clearance to inulin clearance approaches unity. With further decline of the GFR creatinine clearance becomes higher than the corresponding inulin clearance. Thus at a low GFR the creatinine clearance overestimates the true GFR. On the other hand, urea clearance tends to underestimate GFR when the renal function declines. Although the creatinine and urea clearances correlate well with inulin clearance when the GFR is below 15 ml. per minute, it has been shown that the correlation is even better when the mean of simultaneously determined urea and creatinine clearances is taken.^{25, 26}

SUMMARY

No single clinical test of renal function is sufficiently accurate or reliable. In any clinical setting, several tests must be done to assess the overall function of the kidney. Serial tests are more reliable and meaningful than single estimations. The concentration test is most useful when there is mild renal impairment. It is of little value when there is moderate to severe renal failure, and may be harmful. The 15 minute PSP test is useful in early renal insufficiency and is preferred in selected patients for its safety, simplicity, and reliability. The concentration and PSP tests have an added advantage in that one person can carry out the procedures, thus minimizing errors inherent in the other tests. Serial serum urea and creatinine estimations are useful in mild to moderate and advanced renal failure. Urea and creatinine clearances are reliable when the serum levels are not elevated, provided that short clearance periods are elected to avoid inaccuracies in urine collections, postural changes, and variability in urine volumes. In advanced renal failure the mean of simultaneously determined urea and creatinine clearances is preferred. In patients with abnormalities of the outflow tract, serum levels of urea, creatinine, and PSP are satisfactory.

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Urinalysis and the Urinary Sediment

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The future of laboratory medicine is concerned with two goals. First, information will be transferred to computers to be correlated for storage, manipulation, and display to the physician. To provide accurate and significant information for the use of computer methods, new laboratory techniques are being designed. Secondly, since modern medicine will be more involved than in the past with early detection and prevention of chronic disease, the laboratory must respond with appropriate, rapid, simple, and accurate detection techniques for screening large populations. Workers in urinalysis now must be concerned with the development of new and more accurate quantitative techniques.

This paper on urinalysis is concerned not only with describing some present techniques used in the urinalysis laboratory, but also with suggesting some reasonable approaches for the future. Eventually we will come to the point where all the appropriate measurement of dejecta excreted in the urine will be measured quantitatively, and many are working toward that goal. In this article topics selected for discussion include examination of the sediment, made much more precise and useful by combining techniques such as quantitative phase microscopy, special stains, membrane filtration, and clean-voided collection of specimens; improvements and additions to dipstick techniques; cytologic screening for neoplasms in the kidney and urothelium; and identification and quantitation of enzymes and proteins in the urine.

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PHASE CONTRAST MICROSCOPY IN EXAMINATION OF THE URINARY SEDIMENT

Some of the best descriptions of the formed elements of the sediment were written over a hundred years ago by Bright, Bird,⁶ Purdy,⁵⁶ and others. The microscopic methods used to study the urinary sediment have also changed very little in the last century. Unfortunately, the exciting technical developments in microscopy have been ignored in the routine study of the urinary sediment. The phase contrast microscope, invented by Zernicke⁷⁰ in 1934, and the interference contrast microscope, invented by Smith⁶³ in 1947 and developed by Normarski⁴⁷ in 1955, are both relatively new and valuable instruments for the study of unstained sedimentary material.

We have worked with phase contrast microscopy¹¹ and have clearly demonstrated its value for routine and rapid study of the urinary sediment. The method is easy to use, saves time, and allows one to recognize cells, casts, and other dejecta in the urine with a new order of precision and accuracy.

When urinary sediment is viewed through a brightfield microscope, there is a lack of precision owing to the optical limitations of the instrument. The formed elements of the sediment—the casts—are the most important to recognize, but the most difficult to see (Tables 1 and 2). The matrix of all casts is Tamm Horsfall⁴² urinary mucoprotein, which has the same or a very similar refractive index as urine. Therefore, hyaline casts, which are nearly all Tamm Horsfall mucoprotein, are invisible or, at best, extremely difficult to recognize.

Phase contrast microscopy permits visualization of transparent particles by magnifying and translating phase differences into amplitude differences which the eye can recognize.^{57, 62} Because of the excellent visualization and definition of the elements of urinary sediment, especially the matrix of the cast, greater accuracy in differential diagnosis can be achieved.

Not only are the hyaline casts clearly visible (Figs. 1 and 2) with phase contrast microscopy, but maximum definition is not sacrificed, and other elements of the sediment are readily identified. Red blood cells, either free (Fig. 2) or in a cast (Fig. 7), are easily distinguished, appearing as solid gray bodies or solid gray rings.

Recognition of white blood cells (Figs. 3 and 4) is improved because their lobulated nuclei are usually seen and can be more readily distinguished from the round nuclei of small epithelial cells, with which they are often confused when light microscopy is used (Fig. 13). If the urine is acidified, this difference is even more striking. Brownian movement within the white blood cell is immediately obvious.

White blood cell casts (Fig. 6) are also separated from epithelial cell casts (Fig. 14) with greater accuracy because the nuclei of the cells are clearer. In mixed casts, such as white blood cell and epithelial cell casts, the distinction between the cells is occasionally difficult, and an appropriate peroxidase staining method is helpful. Granular casts (Fig. 5) are quite dramatic, and the difference between coarsely and finely gran-

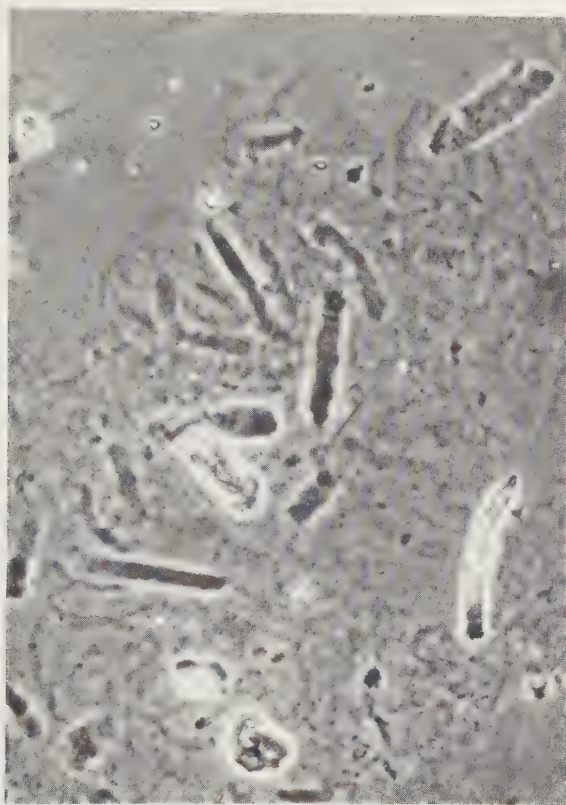


Figure 1. Hyaline casts, epithelial cells, and mucus threads. Phase contrast; $\times 100$.

ular casts is easily seen. Waxy casts are immediately obvious as the photographs demonstrate (Figs. 8 and 9).

Bacteria also appear much more vividly (Fig. 15). They are black, and their morphology is much clearer. They are easily discerned from various forms of small amorphous crystals.

Oval fat bodies, either free (Fig. 10) or incorporated into a cast (Fig. 11), are much brighter.

It is our belief, therefore, that phase contrast microscopy should be used for the routine microscopic study of urinary sediment of patients both in the physician's office and in the hospital laboratory because of the greater morphological accuracy it affords.

In the past, much emphasis has been placed on the occurrence of various crystals in the urinary sediment. However, the occurrence of crystals is of very little clinical significance except in certain instances, such as the formation of stones in the urinary tract, or the indication of rare metabolic disorders by the presence of cystine,⁸ leucine, or tyrosine crystals. Under ordinary circumstances, the positive identification of crystals is not a worthwhile endeavor. On the other hand, it is very important to dissolve these crystals, especially the amorphous crystals,

Table 1. *Clinical Significance of Cells, Bacteria, and Fat in the Urinary Sediment*

CELL	APPEARANCE	ORIGIN	NORMAL VALUES	CLINICAL SIGNIFICANCE
Red	Solid gray biconcave disk or solid gray ring	Anywhere in the genitourinary tract	Prescott: ³⁵ males—38,000/hr. females—28,800/hr. Addis: ¹¹ 0-66,000/hr.	Disorders of genito- urinary tract Systemic diseases Extraordinary pathology Drugs: anticoagulant therapy, birth control pills, large doses of aspirin
White	Granular cells with lobulated nucleus; occasion- ally, granules show Brownian movement; occasionally cells have pseudopods. Stain purple with Prescott-Brodie stain	Anywhere in the genitourinary tract	Prescott: male—28,700/hr. females—107,800/hr.	Urinary tract infection Noninfectious inflamma- tory disease
Renal epithelial	Granular cells with oval nuclei	Kidney	Addis: normal for WBC's and epithelial cells: 750-330,000/hr. Prescott: males—78,200/hr. females—68,000/hr.	Large doses of aspirin Recovery from acute tubular necrosis Tubular damage from a variety of causes

Bacteria	Solid gray rods or chains of cocci	Anywhere in genitourinary tract	Clean-voided midstream specimen should be sterile	10 or more bacteria per high power field correlates with a positive culture of 10 ⁵ dilution.
Oval fat bodies	Brightfield microscopy: dark globules with shiny edge Phase contrast microscopy: bright shiny globules Polaroid lenses: birefringent "maltese cross"	degenerated ²⁸ fat-filled tubular cells		Nephrotic syndrome Diabetic glomerulosclerosis
Other fat				Fabrey's Disease Fractures

Table 2. *Clinical Significance of Casts in the Urinary Sediment*

TYPE OF CAST	APPEARANCE	COMPOSITION	ORIGIN	FORMATION DUE TO	CLINICAL SIGNIFICANCE
Hyaline	Clear cylinders	Tamm-Horsfall mucoprotein	Distal tubules	Rate of urine flow Urinary pH Degree of protein Sodium depletion	Few casts may be seen in normal patients
Red cell	Clear cylinders filled with red blood cells, occasionally orange-red in appearance	Tamm-Horsfall mucoprotein and red blood cells	Distal tubules	Renal parenchymal disease	SLE Acute glomerulonephritis SBE Renal vein thrombosis
White cell	Clear cylinders filled with white blood cells (Prescott-Brodie stain required)	Tamm-Horsfall mucoprotein and white blood cells	Distal tubules	Renal infection Noninfectious inflammation	Pyelonephritis SLE Interstitial nephritis
Epithelial cell	Clear cylinders filled with renal epithelial cells	Tamm-Horsfall mucoprotein and renal epithelial cells	Distal tubules	Sloughing of tubule epithelial cells	Recovery from ATN Tubular damage from a variety of causes

Granular	Cylinders of coarse or fine high refractive particles	Possible re-generation of cellular casts	Distal tubules	Usually associated with renal parenchymal disease
Waxy	Cylinders of smooth highly refractive material	Possible de-generation of granular casts	Distal tubules	Renal parenchymal disease
Fatty* (oval fat body)	Clear cylinders filled with oval fat bodies	Tamm-Horsfall mucoprotein and cholesterol ester crystals	Distal tubules	Tubule fatty change Nephrotic syndrome Diabetic glomerulosclerosis
Broad	All broad casts are similar to narrow casts except they are formed in the collecting tubules instead of the distal tubules and are seen in end-stage kidney disease.			

*Must be identified under polarized light

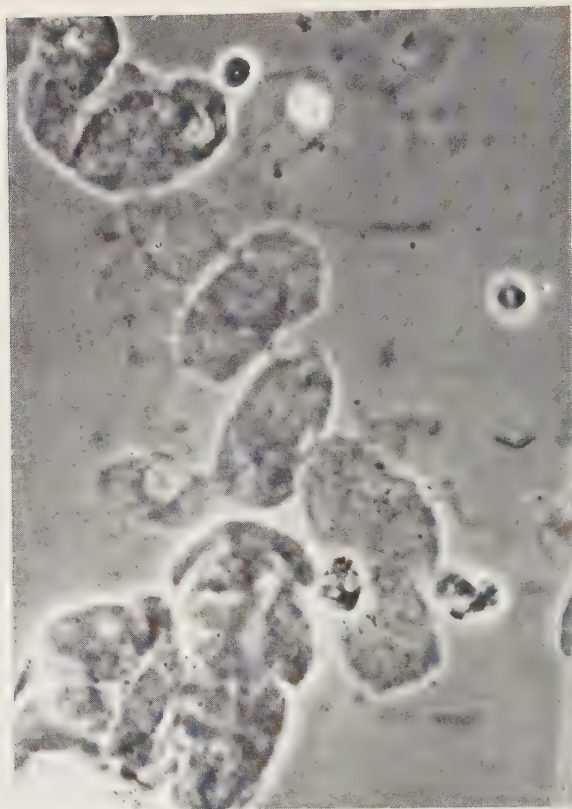


Figure 2. Hyaline casts (center), red blood cells (upper right), white blood cells (lower right). Phase contrast; $\times 400$.

in the urinary sediment, so that they will not interfere with microscopic examination for cells and casts. This is easily accomplished by placing a test tube of urine in a 37°C . water-bath for 10 minutes. Crystals should be dissolved prior to centrifugation.

Quantitation of Formed Elements in the Sediment

Addis,^{1,2} in 1925, was the first to try to quantitate the formed elements in the sediment. However, there are problems with his method. These include cell and cast degeneration during a 12 hour collection, the inability to accurately distinguish casts and the differences between white blood cells and epithelial cells with light microscopy, and a sampling error due to the small amount of sediment counted. The following modification of Addis technique is suggested.

COUNTING METHOD FOR URINARY SEDIMENT

1. 10 ml. of a timed urine specimen is centrifuged at 1500 rpm for 10 minutes.
2. The supernatant is discarded and the whole sediment is pipeted onto a phase contrast counting chamber.*

*American Optical Company, Buffalo, New York.

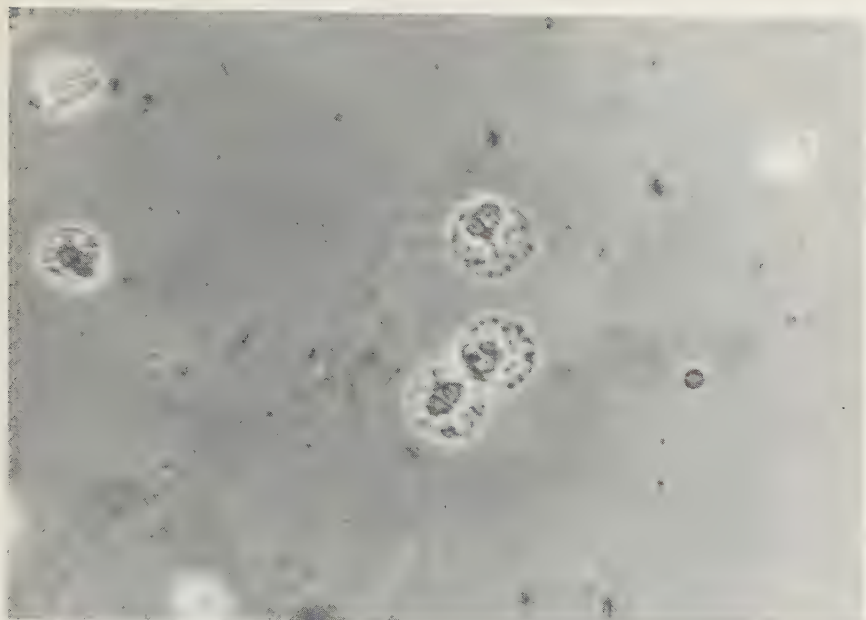


Figure 3. Three white blood cells showing bilobed nuclei and granular cytoplasm (center); two white blood cells (upper left), two red blood cells (right), and mucus threads. Phase contrast; $\times 400$.

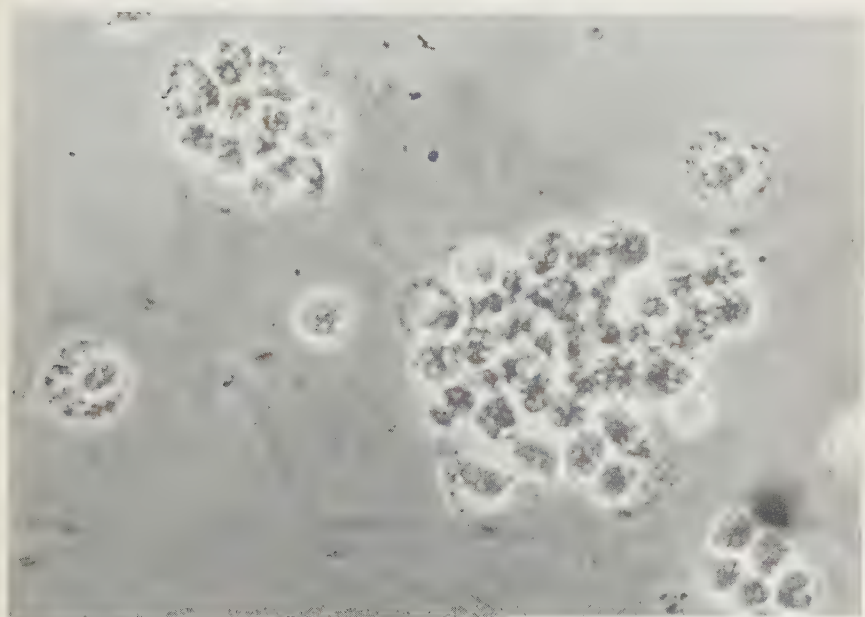


Figure 4. Clumps of white blood cells, two bacterial rods (center top), mucus threads, and amorphous crystals. Phase contrast; $\times 400$.

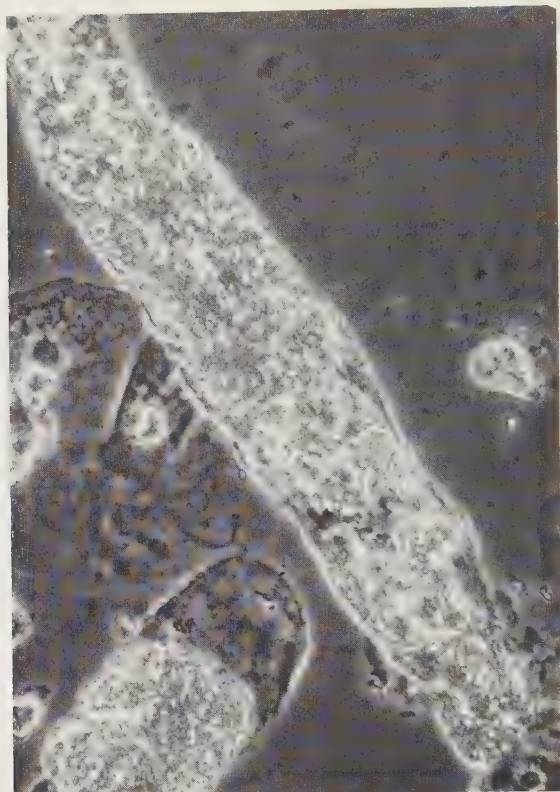


Figure 5. Granular casts (center and lower left), vaginal epithelial cells (left), renal epithelial cell (right center). Phase contrast; $\times 400$.

3. All casts are examined under a low power phase contrast objective. The casts in all nine large squares are counted, and the number of casts is averaged and reported as casts per low power field or casts per 0.1 cu.mm.³
4. All cells and bacteria are examined under a high power phase contrast objective. Five small squares are counted, and the number of cells is averaged and reported as cells per high power field or cells per 0.004 cu. mm.³

Special Stains and Membrane Filtration

Wet staining methods help to distinguish the various cells in the mixed cellular casts.³² We use the Prescott-Brodie stain³⁴ to distinguish chemically and accurately white blood cell casts from epithelial cell casts. This stain is a peroxidase stain and is specific for peroxidase-positive cells such as polymorphonuclear leukocytes. White blood cells stain a deep purple, and red blood cells and epithelial cells stain pink.

With phase contrast microscopy, standardized counting methods, and differential stains, we can interpret, with greater accuracy, frequently encountered formed elements of the sediment. But what about

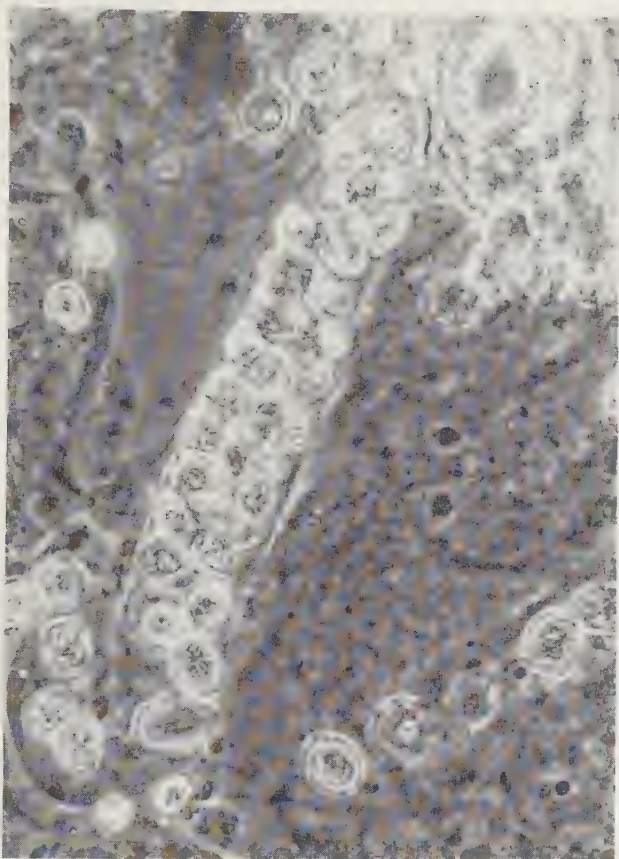


Figure 6. White cell cast (center), mixed epithelial and white cell cast (lower right), two red blood cells (center right), vaginal epithelial cells (upper right), and mucus threads. Phase contrast; $\times 400$.

the rare cells and casts, with diagnostic significance, which are seldom seen in one drop of spun sediment? And what about screening large numbers of specimens for evidence of one type of cell or structure?

Because we were interested in the screening of patients to detect early evidence of chronic inflammatory disease of the kidney, such as chronic pyelonephritis and various forms of interstitial nephritis, we decided to use a membrane filter technique to concentrate the total sediment present in aliquots from random urine specimens. It was then necessary to perfect a reliable, specific, and simple staining technique for screening thousands of urine specimens for white cell casts as evidence of intrarenal inflammation.

Using a membrane filter* to trap all formed elements from the urine specimen,⁶⁶ a staining technique was devised that would specifically stain the polymorphonuclear leukocytes in a prominent color and the hyaline matrix of the casts in a secondary color, so that the white cell casts could be easily distinguished from other casts and from white

*Millipore Corporation, Bedford, Massachusetts.

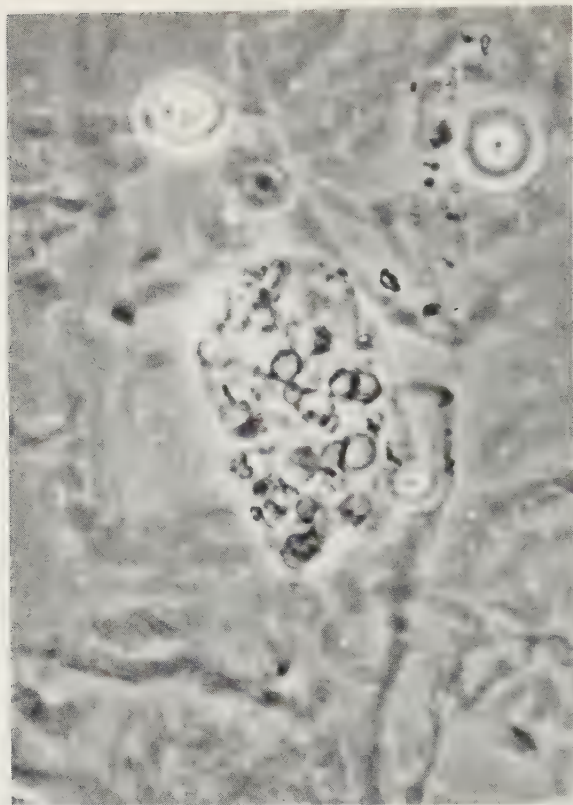


Figure 7. Red blood cell cast (center), mucus threads. Phase contrast; $\times 400$.

cell clumps.^{10, 29} By combining a modified Prescott-Brodie stain with Ponceau S stain on the filter, white cell casts were easily identifiable. The polymorphonuclear leukocytes stained deep purple, while the Tamm Horsfall protein matrix of the cast stained pink. Thereby, white cell casts were distinguished from white cell clumps, which stained deep purple but showed no evidence of a pink-stained cast matrix; from red blood cell and epithelial cell casts, which showed no peroxidase-positive purple cells; and from hyaline, granular, and waxy casts which showed no cells in the cast matrix.

Our studies, soon to be published, have shown that this membrane filter technique is approximately five times more sensitive to the presence of white blood cell casts in the urine than the routine phase contrast counting method. Because of the simplicity of preparation and the rapidity of interpretation, it is our opinion that similar techniques should be developed for different kinds of population studies.

CLEAN-VOIDED COLLECTION OF SPECIMENS

One of the quietest but most significant revolutions in the science of urinalysis has been the introduction of the "clean-voided" collection of

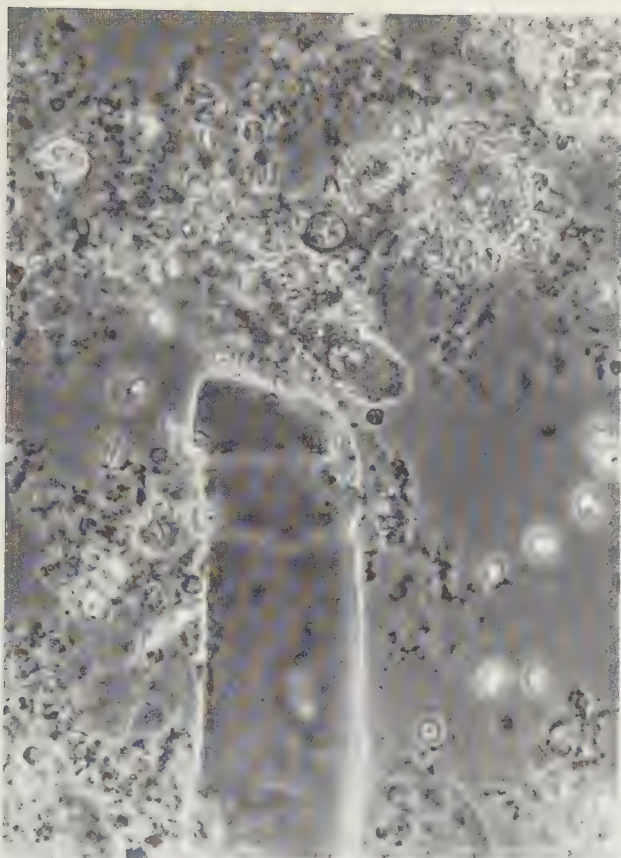


Figure 8. Broad waxy cast (lower center), granular casts (upper center and upper right); many red blood cells and amorphous crystals throughout field. Phase contrast; $\times 400$.



Figure 9. Waxy cast. Phase contrast; $\times 400$.

specimens. It is our firm belief that all urine specimens presented for analysis should be collected from the patient using the clean-voided midstream technique. It has been shown by Beeson,¹ Brumfitt,¹² and Merritt¹³ that obtaining specimens by catheterization risks introducing into the bladder organisms which are themselves capable of producing urinary tract infections. Iatrogenic urinary tract infection occurs in probably 2 to 3 per cent of catheterized patients. It has also been shown by Little¹¹ and Gadeholt²¹ that accurate quantitation of white blood cells and bacteria in the urine requires a clean-voided midstream collection method. If pHisoHex is used as the cleansing agent, care should be taken to rinse it off thoroughly, since pHisoHex has been shown to cause hemolysis of red blood cells in urine if present in large quantities.¹⁴

Not only are clean-voided midstream urine collections convenient and relatively simple to obtain, but large scale screening methods could not be successfully based on catheterized specimens.²⁴

Suprapubic Bladder Aspiration

Suprapubic bladder aspiration has proved to be a safe and reliable method of collecting urine for culture.^{3, 44, 58} Urethral and vaginal contamination are avoided, and a useful specimen for the study of bladder and kidney cytology is presented.

Timing of Specimens

Urine may be obtained at any hour of the day and still yield an adequate sampling for routine urinalysis. One must remember, however, certain types of examinations of the urine are better performed on specimens obtained at certain times of day. For example, a fasting, early morning specimen is less apt to reveal glycosuria than a sample taken 1 to 3 hours after the ingestion of food; a specific gravity determination could better reveal the concentrating ability of the kidney if the specimen examined is the first after a night of water deprivation; and proteinuria is more likely to be found in urine specimens taken after activity than after the patient has been in bed asleep for 8 hours.

The ideal time for a random sample to be collected is in the morning—i.e., the first specimen passed on awakening. This specimen will be more concentrated and will yield a higher number of cells and casts per unit volume.

Timed specimens are most useful in quantitating different parameters, such as total urinary protein, creatinine, urea, glucose, electrolytes, cells, and casts. The most commonly used sample for this is the 24-hour specimen.

The most likely sources of error in collecting timed specimens are failure to collect all the urine passed and inaccurate timing—both of which may invalidate the results obtained.

Twelve-hour and 2-hour timed specimens are popular both with patients and the nursing staff, since the length of time necessary for their participation is shortened. Because of the shorter sampling period, however, any error in collecting or timing is greatly magnified and can lead to grossly inaccurate data. This is especially true for the 2-hour sample.

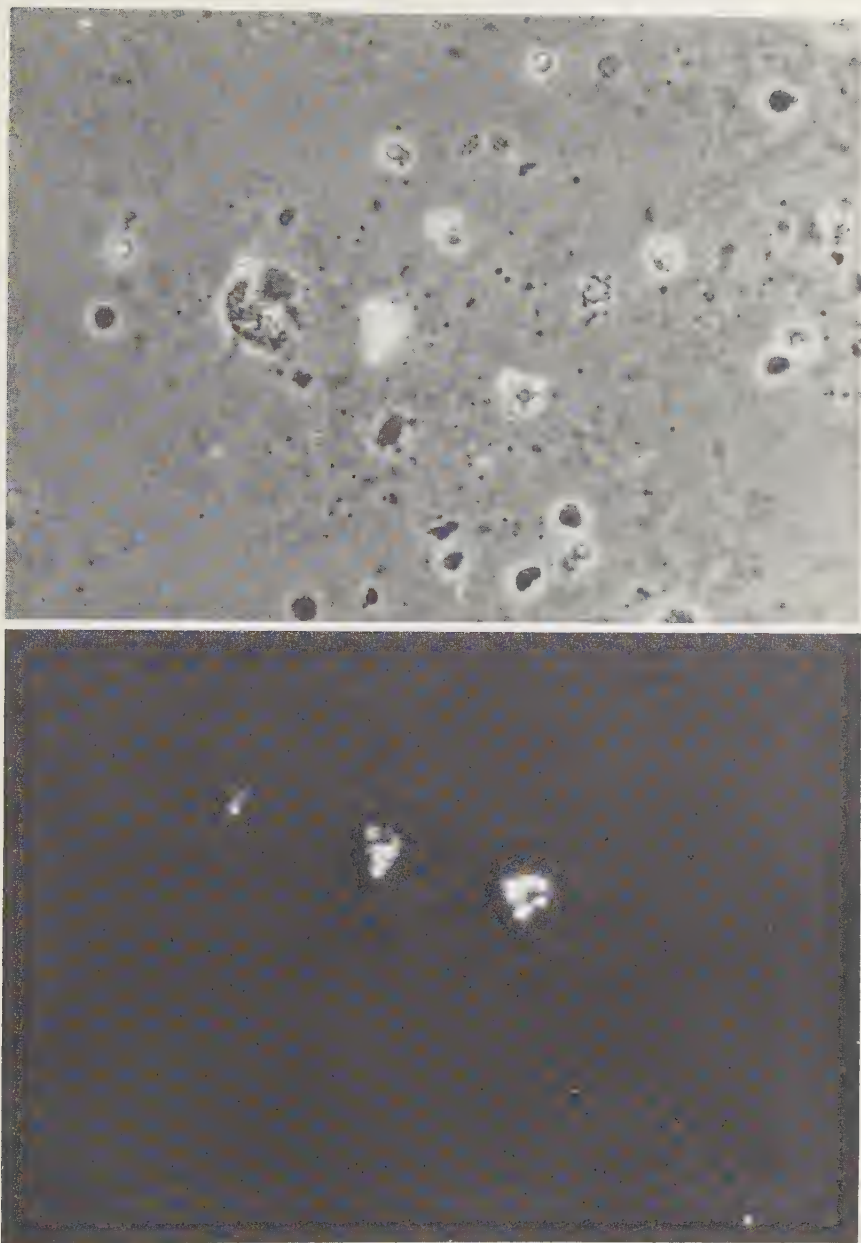


Figure 10. *Above*, Oval fat bodies and red blood cells. Phase contrast; $\times 400$. *Below*, Same field, polarized light; $\times 400$.

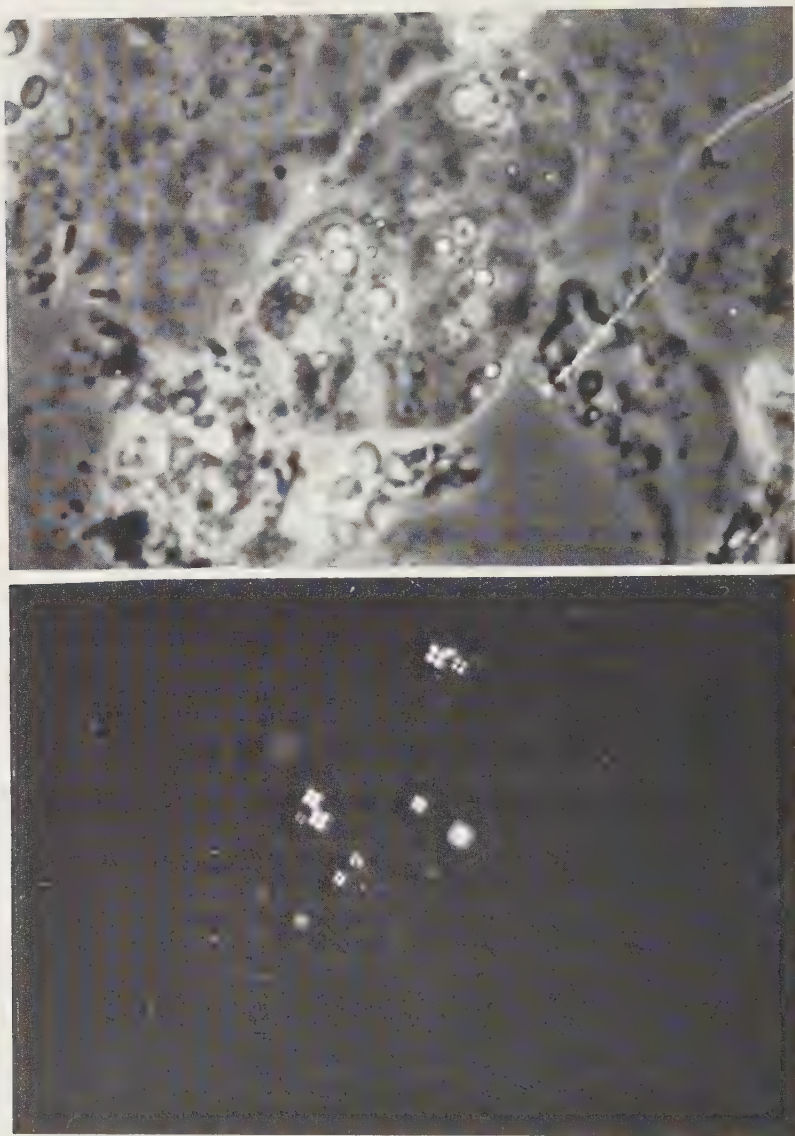


Figure 11. *Above*, Fatty (oval fat) cast (center), yeast (bottom center and upper left), amorphous crystals. Phase contrast; $\times 400$. *Below*, Same field, polarized light; $\times 400$.

Preservation of Specimens

The longer the delay between the time a urine sample is collected and the time the technician works on it, the less reliable the results will be. Urine cultures should be processed immediately. If this is not feasible, they must be stored at 4° C. Even when the specimen is sterile, red blood cells, white blood cells, and casts will survive only in an acid urine with a specific gravity over 1.012. Bacterial contamination adds significantly to destruction of the cells.³⁷ When a long delay between collection and processing for sediment examination is unavoidable, preservatives may be used.⁶⁴ Urokeep* tablets raise the specific gravity and lower the pH. Therefore, the specimen should be divided into two portions; one is kept for chemical analysis, and a preservative tablet is added to the other portion for study of the sediment.²⁷

DIPSTICK TECHNIQUES

Over a hundred years ago nephrologists carried with them small pieces of paper impregnated with ferrocyanic acid and citric acid for home testing of their patients' urinary protein.⁴⁸ Dipsticks have come a long way since that time. It is now possible to test accurately for pH, protein, glucose, ketones, bilirubin, myoglobin, and hemoglobin in a few seconds with one small plastic strip. We will limit our discussion in this paper to the use of the Bili-Labstix.** Information on the use of the classic tests can be found in any clinical laboratory textbook.

The area on the Bili-Labstix devoted to the testing of pH includes the two indicator dyes methyl red and bromthymol blue, and gives a pH reading between 5.0 and 9.0⁶⁹

Protein

The dipstick method is the most commonly used test to detect proteinuria.^{33, 69} The test area is impregnated with tetrabromphenol blue and citrate buffer. Its reaction is based on the phenomenon of "protein error of indicators;" that is, at a certain pH, some indicators will show one color in the presence of protein and another in its absence. The citrate buffer causes the pH of the stick to be about 3, which, in the absence of urine protein, produces a yellow color. When varying amounts of protein are present, the color will become progressively more green.

The stick has the following limitations: (1) it is too sensitive in the trace area, which is positive at 5 to 20 mg. of protein per 100 ml. of urine; (2) it is not sensitive to Bence-Jones protein; and (3) false positive reactions may be obtained in highly alkaline or highly buffered urine.

Glucose

This dipstick is impregnated with glucose oxidase. In the presence of oxygen and glucosoxidase, glucose is oxidated to gluconic acid and

* Standard Reagents Company, 223 North 15th Street, Philadelphia, Pennsylvania

** Ames Company, Division of Miles Laboratories, Inc., Elkhart, Indiana 46514

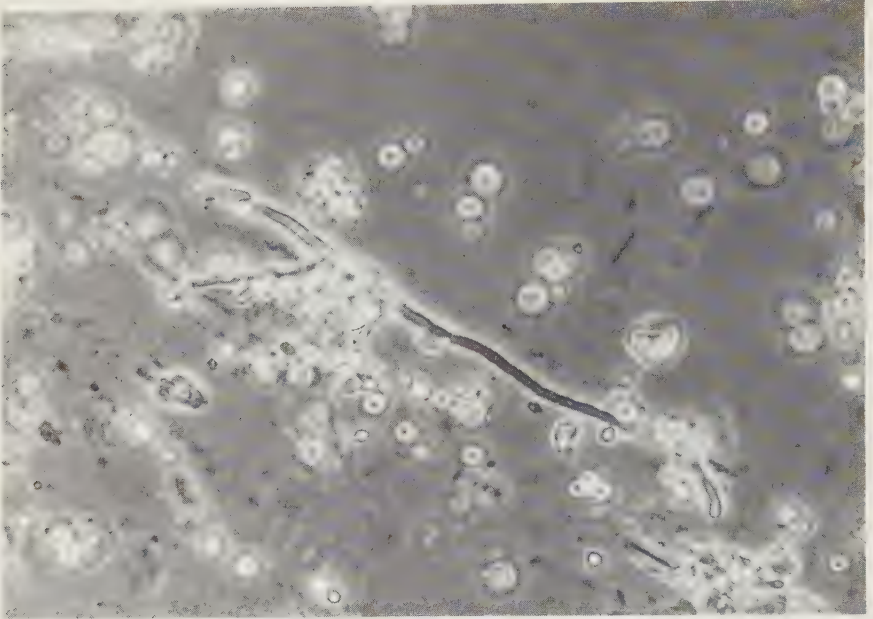


Figure 12. Yeast. Phase contrast; $\times 400$.



Figure 13. Small renal epithelial cells (right). Vaginal epithelial cell (left). Phase contrast; $\times 400$.

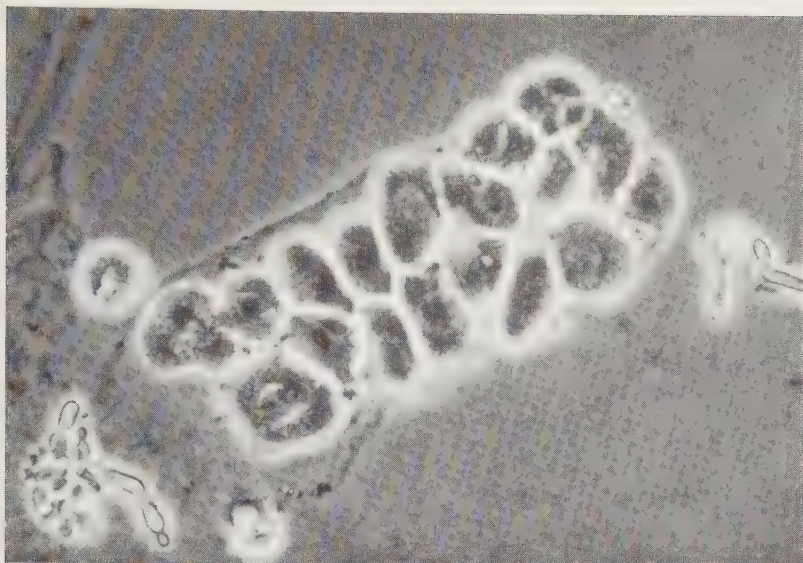


Figure 14. Epithelial cell cast, yeast (right center and lower left). Phase contrast; $\times 400$.

hydrogen peroxide. The hydrogen peroxide, in the presence of peroxidase, then oxidizes the chromogen system on the stick to a shade of purple.

This test is quite sensitive and can detect amounts of glucose as small as 0.1 per cent. False negative tests may occur when large amounts of ascorbic acid are present such as in therapeutic doses of vitamin C or in parenteral preparations of certain drugs, such as tetracycline, which contain vitamin C. False positives may occur if the urine is contaminated with bleach or hydrogen peroxide.

Ketones

There are several tests available for the detection of ketone bodies. Because of their ready availability, widespread usage, and general acceptance, we shall discuss only the Ketostix.⁴⁶ It is based on the chemical reaction of either blood or urine containing ketone bodies with nitroprusside in the presence of glycine, which produces a color ranging from lavender to deep purple. These tests allow detection of as little as 5 to 10 mg. per 100 ml. of acetoacetic acid. It is of interest but not of major clinical importance to recall that this test is less sensitive to the presence of acetone and does not react at all with beta-hydroxybutyric acid.

Hemoglobin and Myoglobin

Another commonly used and useful screening test is that which detects myoglobin and hemoglobin. Myoglobin is rarely found in urine, and when it is, it is usually confused with hemoglobin because the screening tests employed react to both.^{7, 28, 50} It is important to remember that the tests presently employed to detect hemoglobin are more sensitive to free hemoglobin than to intact red blood cells.

The commonly used method for the detection of hemoglobin and myoglobin is Hemastix. Reactions are based on the peroxidase properties of hemoglobin and myoglobin, which cause the release of oxygen from the reagents present. The released oxygen oxidizes orthotoluidine to a blue derivative. The sensitivity of the test is reduced in the presence of high concentrations of ascorbic acid. Contaminants such as hypochlorites may give a false positive result.

Bilirubin

The Bili-Labstix or Ictostix has an area impregnated with stabilized, diazotized 2, 4-dichloroaniline, which turns brown in the presence of bilirubin. In urine, positive readings occur in the presence of 0.2 mg. of bilirubin per 100 ml. or above. The stick may give a reaction which may be read as a false positive in a patient receiving large doses of chlorpromazine.

Specific Gravity and Osmolality

The frequently inaccurate urinometer has now been replaced in the urinalysis laboratory by the temperature-compensated hand refractometer which can give specific gravity readings in one drop of urine.⁴⁶

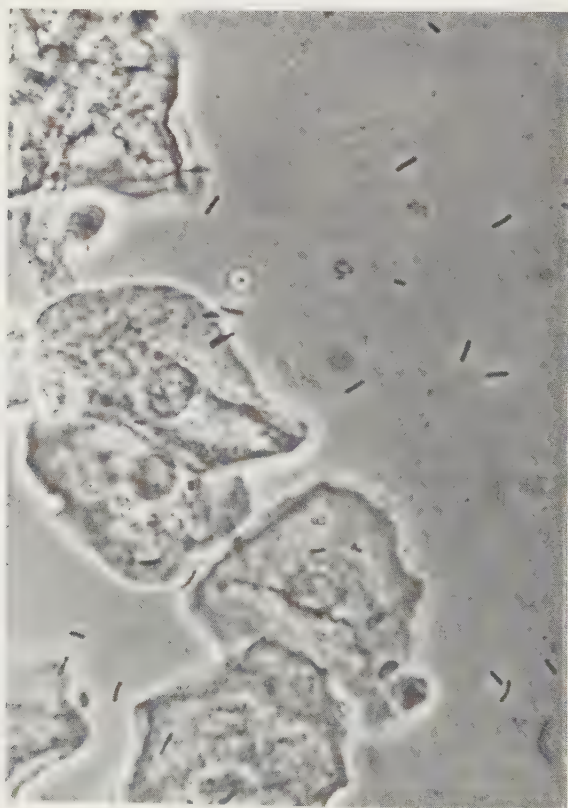


Figure 15. Bacteria and vaginal epithelial cells (left). Phase contrast; $\times 400$.

Osmolality is a measure of the number of particles in a solution, while specific gravity is a measure of the density of the particles. Therefore, when precise information is required as in urine concentration tests or osmolar clearances, osmolality of urine can be rapidly calculated from the freezing point of the urine.

EXAMINATION OF THE URINARY SEDIMENT FOR BACTERIA

There is a high incidence of clinically inapparent infection of the urinary tract in the population.³⁶ Frequently asymptomatic, these infections may have a grave prognosis if they eventually involve the renal system. In an attempt to distinguish between significant bacteriuria and contamination, Kass³⁰ initially found an arbitrary dividing line at about 100,000 bacteria per ml. in adult female patients. This figure has been proven to be an accurate dividing line between infection and contamination in clean-voided urine specimens.

Kunin³⁵ has shown that there is good correlation between microscopic bacteriuria of the spun sediment and the growth of 100,000 colonies. It is therefore incumbent upon urinalysis technicians and laboratories to do more to diagnose asymptomatic bacteria by reporting the presence of bacteria and also noting the absence of bacteria, so that the effectiveness of antibiotic treatment of patients with urinary tract infection can be judged.

URINARY TRACT CYTOLOGY

In 1942, George Papanicolaou described a method of staining cells using 95 per cent ethanol instead of water to dissolve his stains.⁵³ This modification rendered epithelial cells and erythrocytes more transparent, so that more details of nuclei and cytoplasm could be studied. This study began the age of clinical cytology. In 1945 and 1947, Papanicolaou^{51, 52} used his staining method and morphological criteria to determine the presence of cancer cells in the urinary sediment. This approach has been successful^{15, 19, 23, 25} and remains the standard technique by which all new methods of cytological diagnosis of urinary sediment are judged. Fluorescent microscopy⁶⁷ and various simplified staining methods⁶¹ have been used to screen urinary sediment for cancer cells, but with limited success. Thus there remains a need for the development of a simple rapid method by which to screen large populations for the presence of neoplasms of the urinary tract.

We believe that cytological techniques should be used for the study and investigation of all urinary sediment, not just for the diagnosis of neoplasms. The diagnosis of viral inclusion bodies,⁸ neoplastic cells, and other abnormal cells in the urinary sediment can and should be made by the nephrologist as well as the pathologist.

Urinary cytology has been reported to be of assistance in the detection of renal homograft rejection. Various authors have reported an association of specific cell types with clinical rejection. In 1964, Kauff-

man³¹ reported that the presence of large lymphocytes in the urine correlated well with rejection episodes. In 1966, Taft⁶⁵ reported finding large numbers of tubular cells in the urine during acute rejection episodes. On the other hand, Kline³⁴ in 1967 failed to find any particular type of cell in the urine associated with rejection episodes. These observations are of interest, but the clinical usefulness of urinary cytology in renal homograft rejection is yet to be determined.

ENZYMES AND PROTEINS

In order for urinalysis to come of age it must be concerned with achieving a greater sophistication in the identification and quantitation of proteins from the serum and enzymes from the genitourinary tract which are found in the urine.

It has been shown by Berggård⁵ that protein composition in the urine of patients with renal tubule disorders is quite different from that found when renal damage affects predominantly glomerular function. The main difference between the two types of proteinuria is in the average molecular size of the excreted proteins: the average size of the urinary protein is smaller in tubular disorders than in glomerular disorders.

In recent years, immunochemical gel diffusion methods—especially immunoelectrophoresis and radial diffusion immunophoresis—have proven to be valuable tools for the qualitative and quantitative study of individual plasma proteins in the urine. These methods, while quite sophisticated in theory, are relatively uncomplicated in technique and do not require the installation of massive equipment to perform. They can and should be done along with urinalysis, especially when proteinuria is present.

Enzymes found in the urine have been studied with great interest by nephrologists and physiologists. It has been shown,⁶⁸ however, that this endeavor has many limitations: (1) There are many inhibitors of enzymatic activity in the urine. (2) The large molecular weight of most serum enzymes limits their excretion through the glomerulus. (3) Therefore, enzymatic activity in the urine is limited to the enzymes liberated by the turnover and breakdown of renal tubule cells. (4) Although urinary lactate dehydrogenase activity and alkaline phosphatase activity are increased in a wide variety of malignant and nonmalignant diseases of the urinary tract, neither enzyme is specific in differential diagnosis, and merely reflects a nonspecific effect of renal injury.

CONCLUSION

We have attempted to introduce some of the newer methods in urinalysis. It is difficult to predict what changes will be necessary to bring urinalysis into the twenty-first century, but we would like to recommend a few approaches: (1) automatic, rapid chemical analysis of urine, with computerized correlation with body chemistry; (2) automatic morphologic screening techniques of formed elements and cells; and (3)

further investigation of chemical and immunological properties of formed and nonformed elements in the urine.

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